PATENT
454310-5010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

PAOLETTI, ET AL.	)	
	)	
v.	)	Interference 103,399
	)	
MOSS, ET AL.	)	Administrative Patent Judge
	)	Andrew H. Metz
	)	

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231, BOX INTERFERENCE
on March 13, 1995

THOMAS J. KOWALSKI, REG. NO. 32,147
Name of Applicant, Assignee or Registered Representative

Signature

13 Mar 95
Date of Signature

530 Fifth Avenue
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PAOLETTI ET AL. MOTION UNDER 37 C.F.R. §§ 1.633 AND 1.637 FOR JUDGMENT ON GROUND THAT MOSS ET AL. CLAIMS NOT PATENTABLE TO MOSS ET AL.

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX INTERFERENCE

Sir:

PAOLETTI ET AL. ("Paoletti") hereby move under 37 C.F.R. §§1.633 and 1.637 and any other Rules of the Commissioner for judgment on the ground that Moss et al. claims designated as corresponding to the Count are not patentable to Moss et al.

("Moss"). In particular, the Moss claims corresponding to the Count are unpatentable to Moss under 35 U.S.C. §102/103.

BACKGROUND

Prior to Moss' filing date[1] the knowledge of the skilled artisan included:

recombinant vaccinia virus;

with expression of exogenous DNA therein under vaccinia control;

with exogenous DNA therein deliberately placed proximal to vaccinia promoters;

the 7.5 K promoter;

that the 7.5 K promoter naturally occurs "adjacent" to the coding sequence for the 7.5 K polypeptide; and,

the mapping and identification of the vaccinia virus thymidine kinase gene.

Without inventive effort, one skilled in the art could place desired exogenous DNA proximal to a vaccinia promoter; could place a desired promoter, such as the 7.5 K promoter, adjacent to coding DNA, as such occurs naturally with respect to the 7.5 K promoter and coding sequence for the 7.5 K polypeptide;

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[1] Paoletti respectfully asserts that Moss' claim of priority under 35 U.S.C. §120 to any of application Serial Nos. 06/555,811, filed November 28, 1983, and 06/445,892, filed December 1, 1982 and 06/445,451, filed November 30, 1982 should not be sustained because of the failure to comply with Section 112 of Title 35, as discussed in the accompanying Paoletti Motions, incorporated herein by reference. For the sake of argument only, and without any prejudice or admission, entitlement by Moss to the benefit of these applications is assumed. However, Paoletti invites the APJ and Board to consider as prior art to Moss art dated after November 30, 1982, including Paoletti et al., U.S. Patent No. 4,603,112, issued from application Serial No. 06/446,824, filed December 8, 1982. "Adjacent" is not defined in any Moss application, but it is used in the art; see Venkatesan, Cell, 125:805-13, 1981 (Exhibit 1).

and, could locate the vaccinia virus TK promoter by looking to sequences upstream from the mapped and identified gene therefor, since promoters for other vaccinia virus genes, such as for the 7.5 K polypeptide, were known to be adjacent to and upstream from the gene.

Further, it is clear from the art that contrary to Moss' arguments, deliberately employing or purposefully placing vaccinia transcriptional regulatory sequences (or a vaccinia promoter) to control expression of the foreign gene in a recombinant vaccinia virus such as by inserting the vaccinia regulatory sequence into the vaccinia virus along with the foreign gene was within the ambit of the skilled artisan (particularly considering that expression under vaccinia control and by endogenous vaccinia promoter in recombinant vaccinia virus was in the art) and, was a simple duplication of that which had already been disclosed, particularly as naturally occurring with respect to the 7.5 K polypeptide gene and the promoter therefor (see, e.g., Venkatesan, Exhibit 1).

The exogenous DNA in Panicali et al., PNAS, 79: 4927-4931, August 1982 (Exhibit 2) (the "Panicali et al. PNAS article") and Paoletti et al., U.S. Patent No. 4,769,330 (the '330 Patent, Exhibit 3) was expressed under vaccinia control and was not fortuitously-proximal to a vaccinia virus promoter as asserted by Moss. Note that, as discussed below, the '330 Patent expressly teaches that expression of the exogenous DNA was under

vaccinia control and that the insert could include a promoter (see col. 2, line 63 to col. 3, line 1 and, col. 10, lines 7 to 10), and, that the Panicali PNAS article teaches and suggests at page 4931 that vaccinia signals are operative. Note also the Abstract at page 55 ("the Panicali et al. Abstract") and the corresponding presentation by Drs. Panicali and Paoletti at the September 20-23, 1982 Poxvirus-Iridovirus Workshop held at Cold Spring Harbor Laboratory, Cold Spring Harbor, New York (the "Paoletti laboratory CSH presentation") (a copy of which is attached Exhibit 4) and the corresponding presentation on August 4, 1982 during the American Society for Virology (ASV) Conference held at Cornell University, Ithaca, New York, August 2-5, 1982 ("The Panicali et al. ASV presentation") (a copy of the program for which (including its title) is attached as Exhibit 5) wherein it was disclosed that "endogenous vaccinia promoters" were

operative in expression in recombinant vaccinia virus.[2]

Note too Moss' arguments in the January 27, 1993 Preliminary Amendment in USSN 07/987,546, at 12 to 15 (copy attached as Exhibit 6). At page 13 Moss argued that Wittek et al, Cell 21: 487-93 (1980) and other references (including Venkatesan, Cell, 125: 805-13 (1981); Exhibit 1) provide guidance with regard to mapping RNA start codons. At page 14, Moss asserted that "[t]he method of determining the precise location of a promoter and for testing of a promoter's suitability . . . was within the skill of the art [and that t]he uncertainties . . . [have] no bearing on the positive understanding of certain

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[2] The prior art nature of the Panicali et al. Abstract, the Paoletti Laboratory CSH presentation and the Panicali et al. ASV presentation was, on information and belief, called to Moss' attention by the Opposition to the Moss European Patent and Application, prior to Declaration of this Interference, and was not called to the U.S. Examiner's attention. Despite Moss' bogus claim of confidentiality before the EPO with respect to the Poxvirus - Iridovirus Workshop (see Exhibits 21-28), it is respectfully submitted that it was nonetheless incumbent upon Moss under 37 C.F.R. §1.56 to place the information before the U.S. Examiner so that she might determine availability as prior art of the Panicali et al. Abstract, the Paoletti Laboratory CSH presentation and the Panicali et al. ASV presentation and patentability over that art before any allowance of Moss' claims. Simply, Moss never removed the Panicali et al. Abstract, the Paoletti Laboratory CSH presentation and the Panicali et al. ASV presentation as prior art (note the views of Drs. Mackett and Buller; see Exhibit 28). Pursuant to 37 C.F.R. §1.639, Paoletti seeks discovery as to all evidence concerning, relating to or referring to the decision not to call to the U.S. Examiner's attention the Panicali et al. Abstract, the Paoletti Laboratory CSH presentation and the Panicali et al. ASV presentation, including testimony of witnesses who executed Declarations for Moss regarding their bogus claim confidentiality, and, of all persons who elicited those Declarations, and all documents concerning, relating to and referring to the ASV conference, the September 20-23, 1982 Workshop, that decision or that bogus confidentiality claim. In this regard, it is noted that one of those witnesses was Dr. Panicali. His Declaration was signed after the Declaration of this Interference, and on information and belief, attorneys from Foley & Lardner were in contact with him, in possible violation of 37 C.F.R. §10.87. Full investigation thereof is also respectfully requested. If necessary, this Paper can be construed as a Motion for an immediate testimony period concerning that which is available as prior art against Moss.

tools such as RNA mapping. Moss further argued that, "it was generally accepted at the time of [their] application that there are a large number of vaccinia virus mRNAs and promoters." And, at page 15, Moss admitted:

> [Q]uite a lot was known about the characterization of early and late genes . . . For instance, it was known that both early and late viral mRNAs have capped 5' ends.
> . . . The approximate genome locations of many early and late mRNAs had been determined already. . . . A general method of precisely locating RNA 5' ends that does not depend on prior knowledge of promoter sequence or structure was available.
> . . . Thus, one skilled in the art at the time of the invention could have found additional promoters based upon existing knowledge.[3]

The invention by Paoletti et al. of a recombinant vaccinia virus as fully disclosed in the '330 Patent, (i.e., a vaccinia virus synthetically modified to contain exogenous DNA in a nonessential region of the vaccinia virus genome), and particularly such a virus which has expression under vaccinia control, was not taught or suggested by art pertaining to other

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[3] However, at page 6 of application Serial No. 07/072,455 Moss asserts that the nucleotide sequence and a precise translational map of the promoter is needed to practice Moss. Thus, for enablement reasons, Moss' claims should be limited to specific promoters (i.e., Moss' present claims are not enabled under 35 U.S.C. §112, first paragraph) or, Moss' arguments about the state of the art should be employed as admissions under 35 U.S.C. §102/103, and as combinable with other Section 102/103 art. Note too that the Moss claims 39 and 50, by not calling explicitly for the vaccinia TK or 7.5 polypeptide promoters but rather for that "which regulates" the TK gene, a 7.5 kd polypeptide may also be overbroad. See also Exhibit 9 (charts showing the change in "promoter", "foreign gene", "adjacent to" and "chimeric gene" definitions from USSN 06/445,451 to 06/072,455).

vectors. However, the knowledge in the art in 1982 pertaining to the use of promoter elements for expression of heterologous genes using defined, translocated promoter elements can be used in combination with the art discussed above to further evaluate the novelty and nonobviousness of the Moss claims and to also evaluate the credibility of the assertions of Moss (since by each of the '330 Patent the Panicali et al. PNAS article, the Panicali et al. ASV presentation, the Panicali et al. Abstract and the Paoletti laboratory CSH presentation, a recombinant vaccinia virus having expression of exogenous DNA by use of a vaccinia promoter as, by 1982, part of the state of the art).[4] Note Moss' citation in the June 18, 1990 Preliminary Amendment in USSN 07/539,169 at 8 to 9 (copy attached as Exhibit 7) to Post and Roizman, Cell, 25:227-32 (1981) regarding "the use of homologous flanking segments to facilitate incorporation of a polynucleotide into a viral genome" as being well-understood, and, that Post and Roizman (copy attached as Exhibit 8), and other art (see Paoletti Declaration, Exhibit 27) demonstrate that Moss' alleged methodology was an obvious variation of the vaccinia virus prior art, when it is fully considered. Moss' citation to Post and Roizman should be taken as an admission by Moss of the

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[4] Note that during the prosecution of USSN 334,456, herpes virus was deemed patentably distinct in the judgment of no interference-in-fact with Roizman et al., whereby U.S. Patents Nos. 4,769,330 and 4,769,331 to Paoletti et al. and Roizman et al., respectively, issued.

applicability of that document as to Moss (but not Paoletti; see note 4).

Accordingly, Moss' arguments and claim recitations, including the "adjacent to" recitation and "chimeric gene" concept for plasmids, recombinant vaccinia virus and for methods for preparing a vector and for producing a protein (e.g., Moss claims 33, 44, 55 and 57 and, claims dependent thereon) do not render the claims patentable over the prior art.[5]

ARGUMENT

THE MOSS CLAIMS

Moss claims 33, 36, 37, 39, 41, 42, 43, 44, 47, 48, 50, 52, 53, 54, 55, 56 and 57 of application Serial No. 07/987,546, filed December 7, 1992[6] were designated as corresponding to the

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[5] Note that the limitations of canceled Moss claims 34, 35, 43, 46 and 58-60 assumed by the Examiner to be either within or excluded by the term "adjacent" are not explicitly included in or excluded by the claims, and were not intended to be, as shown by the scope of original claims 1, 2 and 7 of USSN 07/072,455 (e.g., only claim 7 including the limitation "which in nature are not contiguous with the vaccinia" promoter) and the June 18, 1990 Preliminary Amendment in USSN 07/539,169, at pages 11 to 12, especially footnote 2, wherein the limitations of "no other TRS poxvirus structural sequence . . . interposed between the recited poxvirus TRS and the 'first DNA sequence'" in dependent claims was asserted to be a special, particular form of "adjacency". Note further that claims 37 and 48 call for the promoter to be not contained within the non-essential region, thus allowing claims 33 and 44 to read upon plasmids and recombinants containing a promoter, such as Paoletti et al. vP2, vP4 and vP6, contrary to Moss' arguments and chimeric gene methodology. Similarly, Moss' claim 44, in view of claim 48, allows for a recombinant vaccinia virus from insertion of only exogenous DNA with flanking vaccinia DNA and not from insertion of Moss' chimeric gene (because the vaccinia promoter can be in the non-essential region, prior to insertion, contrary to Moss' arguments regarding the prior art and Moss' chimeric gene concept).

[6] USSN 07/987,546 was filed as a continuation of application Serial No. 07/539,169, filed June 18, 1990, as a continuation of application Serial No. 07/072,455, filed June 13, 1987 as allegedly a continuation-in-part of applications Serial Nos. 06/555,811, 06/445,892 and 06/445,451; application

Count, Moss claim 44. A copy of these claims is attached as Exhibit 10.

Moss claims 33, 44, 55 and 57 are independent claims. Moss claims 33, 36, 37, 39, 41, 42 and 43 are directed to a plasmid. Moss claims 44, 47, 48, 50, 52, 53 and 54 are directed to a recombinant vaccinia virus. Moss claims 55 and 56 are directed to a method for preparing a vector. And, Moss claim 57 is directed to a method for producing a protein. Moss claims 33 and 44 are not limited by the method of claims 55 or 56 and, Moss claim 44 is not limited to a plasmid of claim 33, or to such a plasmid prepared by a method of Moss claims 55 or 56. Thus, Moss claim 44 can read upon placing a foreign gene under vaccinia control due to an endogenous promoter.

All of the Moss claims include the term "adjacent to", and this recitation was relied upon in an attempt to distinguish over the '330 Patent, as shown by attached Exhibit 11, pages 11 to 13 of the June 18, 1990 Preliminary Amendment is

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Serial No. 06/555,811 was allegedly a continuation-in-part of application Serial No. 06/445,89; and application Serial No. 06/445,892 was allegedly a continuation-in-part of application Serial No. 06/445,451. Moss was accorded benefit of all of these applications. Presence of "adjacent to" and its meaning (vis-a-vis "chimeric gene", "foreign gene" and "promoter", in which context "adjacent to" is used) in the four Moss specifications is shown in the charts in Exhibit 9, together with dictionary definitions of "next to", "adjacent to" and "contiguous" to demonstrate the lack of enablement, failure to satisfy the description requirement, and the vagueness and indefiniteness of Moss' claim language, and, that the Moss claims are not entitled to a date earlier than that of USSN 07/072,455, especially since the length of the "adjacent" pieces of DNA changed in the applications, as did the description of where the promoter is not located. Moss should not be entitled benefit of any application earlier than USSN 07/072,455.

USSN 07/539,169, pages 10 to 17 of the March 2, 1992 Amendment in USSN 07/539,169, pages 2 to 3 of the June 24, 1992 Office Action in USSN 07/987,546 and pages 2 to 4 of the October 22, 1993 Amendment in USSN 07/987,546. However, the term "adjacent to" is undefined and has had variable meanings in Moss' applications (see Exhibit 9); the Examiner relied upon a layman's dictionary definition (rather than the art, e.g., Venkatesan, Exhibit 1); and, to contrast with the Paoletti et al. PNAS article, Moss urged that their "construct within the present invention includes a poxvirus TRS purposefully placed in a predetermined relation to a polypeptide - encoding sequence" (Exhibit 11, June 18, 1990 Preliminary Amendment at 12-13).

As shown in Exhibit 9, "adjacent to" does not necessarily exclude "some vaccinia coding sequence, between the endogenous vaccinia promoter and the foreign coding sequence" as interpreted by Examiner Mosher, because, for instance, how would claims 36 and 47 then limit claims 33 and 44? By calling for "consists essentially of", the term "adjacent to" in Moss claims 33 and 44 is open-ended to include additional DNA. Note also that the definition of promoter in USSN 06/445,451, as DNA preceding and including the site at which RNA synthesis begins, allows for additional vaccinia DNA before, as well as after, the site at which RNA synthesis begins, in contrast to the shorter length DNA permitted by the broadened "promoter" definition in USSN 07/072,455. Further, since claims 37 and 48 call for the

promoter to not be within the non-essential region, according to the doctrine of claim differentiation, the promoter of claims 33 and 44 therefore may be within the non-essential region; thus permitting the presence of additional DNA, including "some vaccinia coding sequence."

In addition, it is respectfully submitted that Examiner Mosher, in construing "adjacent" in the Moss claims incorrectly applied the dictionary definition for "adjacent" in two ways. Firstly, the concept of "adjacent" as used in the prior art, e.g., Venkatesan (Exhibit 1), should have been used to define "adjacent", not a non-technical dictionary definition of "adjacent".

Secondly, if the dictionary definition is used to define "adjacent" as "the absence of anything of the same kind in between", then Moss' "adjacent" excludes a vaccinia promoter intervening between the recited vaccinia promoter and the recited foreign gene in Moss' claims. Moss' "adjacent" does not exclude extraneous exogenous DNA which, in a vaccinia setting is inoperative but which in a herpes simplex virus setting acts as a promoter (because "promoter" is a functional definition of a particular DNA sequence; if the DNA does not function as a "promoter" it is not a promoter). See also USSN 07/072,455, page 1, line 22 to page 2, line 5 (promoter defined as a sequence which "positively regulate[s] the transcription of a gene", implying that a sequence which does not "positively regulate" is

not a promoter. Accordingly, Moss' application, by its own terms, prevents "adjacent" from excluding the additional inoperative HSV TK DNA of Paoletti's vP2, vP4 and vP6). The dictionary definition of "adjacent", by excluding an intervening vaccinia promoter also does not exclude intervening vaccinia coding sequence. In each of Moss' claims 33, 44, 55 and 57, "said promoter sequence is adjacent to" refers to the earlier recited "vaccinia virus promoter sequence" such that "absence of anything of the same kind in between", according to the dictionary, only excludes an intervening vaccinia virus promoter sequence.

Examiner Mosher also read the limitations of now canceled claims 34, 35, 45, 46 and 58 to 60 as included in or excluded by "adjacent" in independent claims 33, 44, 55 and 57, contrary to Moss' assertions in the March 2, 1992 Amendment (see Exhibit 11) and in violation of the doctrine of claim differentiation.

The presentation of claims 34, 35, 45, 46 and 58 to 60, the arguments concerning these claims, and their cancellation without prejudice or admission, all demonstrate that Moss never intended "adjacent" to exclude intervening DNA coding for that which would act as a promoter in vaccinia or in any other (but not vaccinia) environment (and in the latter instance is not a promoter in vaccinia but only extraneous DNA), or to exclude intervening DNA coding for a vaccinia protein or portion thereof.

If Examiner Mosher believed these recitations were included in or excluded by Moss' independent claims, it is submitted that she should have demanded that they be explicitly included or excluded in the independent claims and not have sought their inclusion or exclusion by reading into the undefined term "adjacent", especially in view of Moss' presentation, arguments and cancellation of claims 34, 35, 45, 46 and 58 to 60, which demonstrate a contrary intention by Moss.

Moreover, as shown by Exhibit 11, Moss' arguments for patentability based upon "adjacency" are premised upon "no vaccinia or other poxvirus promoters had been localized", that there was "no guidance [as] to the placement of the . . . promoter in relation to the polypeptide-encoding sequence", and no suggestion of even including a promoter and a coding sequence (contrast the Moss admission in Exhibits 6 and 7). Indeed, in view of Exhibit 11, it seems that to Moss, "adjacent to" may simple mean "purposefully placed [promoter and foreign gene] in a predetermined relation"; and, this is somehow different from the prior art. However, these arguments are based upon a narrow misreading of the prior art and of Moss' own disclosure.

And, if the term "adjacent to" is intended to exclude any intervening nucleotides (see Venkatesan, Exhibit 1), the Moss application does not describe or enable one skilled in the art to carry out the subject matter of the claims, because the disclosure of the Moss specification is limited to examples

wherein there are extraneous DNA sequences between the vaccinia promoter element and the translation initiation site of the foreign gene, and there is no teaching in Moss that a recombinant vaccinia virus without such extraneous DNA would be operable.

Construction and sequencing of the chimeric genes disclosed by Moss has shown that there are extraneous DNA sequences between the vaccinia promoter and the translation initiation site of the foreign gene. The disclosure of extraneous DNA sequences between the promoter element and translation initiation codon of the foreign gene in the Moss application is as follows:

Example 1: 7.5 K promoter element. The 275bp 7.5 K promoter element contains the vaccinia 7.5 K promoter including the transcriptional start site and 30 bp of vaccinia DNA downstream from the transcriptional start site. The element does not include the vaccinia 7.5 K translational initiation codon (ATG) or 18 bp of vaccinia DNA immediately preceding the ATG (Venkatesan et al. Cell 125:805-813 (1981); copy attached as Exhibit 1). The 7.5 K promoter element was cloned into pUC9 (Messing, in Methods in Enzymology 101:20-78 (1983); copy attached as Exhibit 12) cut with HincII, resulting in plasmid pGS15 and its derivative, pGS19. A promoter element from pGS19 was inserted in both orientations into the EcoRI site within coding sequences of the vaccinia thymidine kinase gene, resulting

in plasmids pGS20 and pGS21. These plasmid vectors were used for the construction of chimeric genes. In all cases, such chimeric genes contain at least 3 bp of extraneous DNA derived from the pUC9 multicloning region and located between the vaccinia transcriptional regulatory element and DNA encoding the foreign gene.

Example 2: Vaccinia TK promoter; plasmids pMM1-4. The vaccinia TK locus was modified for use as an insertion site for the introduction of foreign DNA into the vaccinia genome. The left flanking arm includes the vaccinia TK promoter element for the expression in situ of foreign genes. This promoter element includes the vaccinia TK transcriptional initiation site. The element does not include the vaccinia TK translational initiation codon (ATG) or 3 bp of vaccinia DNA immediately preceding the ATG (Weir and Moss, J. Virol. 46:530-537 (1983); copy attached as Exhibit 13). Chimeric genes constructed in plasmid vector pMM4 contain variable amounts of extraneous DNA derived from the pUC9 multicloning region. This DNA is located between the vaccinia TK transcriptional regulatory element and the DNA encoding the foreign gene.

Example 3: CAT gene. The gene encoding chloramphenicol acetyl transferase (CAT) was identified in E. coli transposons. It is used in E. coli plasmids to confer

chloramphenicol resistance (Cm^r). Plasmid pBR328 (Soberon et al., Gene 9:287-305 (1980); copy attached as Exhibit 14) is a derivative of pBR325. The sequence of the CAT gene (Cm^r gene) common to both plasmids is published (Prentki et al., Gene 14:289-299 (1981); copy attached as Exhibit 15).

A 770 bp TaqI DNA fragment containing the CAT gene was isolated from plasmid pBR328. The TaqI fragment containing the CAT gene was cloned into pUC7 (Messing, 1983) generating plasmid pGS29. The CAT gene was isolated from PGS29 as a BamHI fragment, and inserted into the BamHI site of plasmid pGS21. The resulting plasmid, pGS24, contains the CAT gene under the transcriptional control of the vaccinia 7.5 K promoter. The chimeric gene was inserted into the TK locus of vaccinia virus, resulting in recombinant vaccinia virus vCAT24. In vCAT24 there are 10 bp of extraneous DNA derived from the pUC9 and pUC7 multicloning regions immediately downstream from the vaccinia 7.5 K promoter. Additionally, the vaccinia promoter is separated from the translational start codon of the CAT gene by 30 bp of DNA derived from pBR328. The DNA sequence separating the 7.5 K promoter region and the CAT translational start codon is as follows. Restriction sites are underlined.

BamHI TaqI

5′ GACGGATCCGTCGAGATTTTCAGGAGCTAAGGAAGCTAAA 3′

Example 4: HSV-TK gene. The sequence of the gene encoding the Herpes Simplex Virus thymidine kinase (HSV-TK) and surrounding region is published (Wagner et al., Proc. Natl. Acad. Sci. USA 78:1441-1445 (1981); copy attached as Exhibit 16). A 1.8kb HincII/PvuII fragment containing the HSV-TK coding sequence was cloned into the HincII site of pUC7, generating plasmid pVH4. The HSV-TK gene was isolated from pVH4 as an EcoRI fragment, and inserted into the EcoRI site of pMM4. The resulting plasmid, pMM20, contains the HSV-TK gene under the transcriptional control of the vaccinia TK promoter element. The chimeric gene was inserted into the TK locus of vaccinia virus. In the resulting recombinant vaccinia virus there are 27 bp of extraneous DNA derived from the pUC9 and pUC7 multicloning regions immediately downstream from the vaccinia TK promoter. Additionally, the vaccinia TK promoter is separated from the translational start codon of the HSV-TK gene by 74 bp of DNA derived from HSV. The DNA sequence separating the vaccinia TK promoter region and the HSV-TK translational start codon is as follows. Restriction sites are underlined.

BamHISmaIEcoRI BamHI HincII BglII

5′ GACGGATCCCGGGAATTCCCCGGATCCGTCAACAGCGTGCCGCAGATCTTGGT

GGCGTGAAACTCCCGCACCTCTTTGGCAAGCGCCTTGTAGAAGCGCGT 3′

Example 5: VSV N gene. Plasmid pJS223 contains a cDNA copy of the nucleoprotein (N) gene from vesicular stomatitis virus (VSV) (Sprague et al., J. Virol. 45:773-781 (1983); copy attached as Exhibit 17). In pJS223 the VSV N gene is preceded by a XhoI site derived from synthetic linkers. A XhoI fragment containing the VSV N gene was isolated from pJS223 and inserted into the SalI site of pMM3. The resulting plasmid, pMM17, contains the VSV N gene under the transcriptional control of the vaccinia TK promoter element. The chimeric gene was inserted into the TK locus of vaccinia virus. In the resulting recombinant vaccinia virus the vaccinia TK promoter element is separated from the translational start codon of the VSV N gene by 31 bp of DNA derived from pJS223. The DNA sequence separating the vaccinia TK promoter region and the VSV N translational start codon is as follows.

5′ GAGGTCAGGAGAAACTTTAACAGTAATCAAA 3′

Examples 6 and 7: HBsAg gene. The DNA sequence of the gene encoding the HBV surface antigen (HBsAg) for the adw subtype is published (Valenzuela et al., Nature 280:815-818 (1979); copy attached as Exhibit 18). A 1350 bp BamHI fragment (Moriarty et al., Proc. Natl. Acad. Sci. USA 78:2606-2610 (1981); copy attached as Exhibit 19) containing the coding sequence for the

HBsAg gene was inserted into plasmid vectors pGS20, pGS21 and pMM3, all cut with BamHI.

Plasmids pHBs2 and pHBs4 contain the HBsAG coding sequences inserted in the correct orientation relative to the translocated 7.5 K vaccinia promoter. These chimeric genes were inserted into the TK locus of vaccinia virus, resulting in vaccinia recombinants vHBs2 and vHBs4, respectively. In vHBs2 and vHBs4 there are 3 bp of extraneous DNA derived from the pUC9 multicloning region located immediately downstream from the vaccinia 7.5 K promoter element. Additionally, the vaccinia 7.5 K promoter is separated from the translational start codon of the HBsAg gene by 127 bp of HBV DNA. The DNA sequence separating the 7.5 K promoter region and the HBsAg translational start codon is as follows. Restriction site is underlined.

BamHI

5′ GACGGATCCCAGAGTCAGGGGTCTGTATCTTCCTGCTGGTGGCTCCAGTTCAGGAAC
AGTAAACCCTGCTCCGAATATTGCCTCTCACATCTCGTCAATCTCCGCGAGGACTGGGGA
CCCTGTGACGAAC 3′

Plasmids pHBs5 contains the HBsAg coding sequences inserted in the correct orientation relative to the vaccinia TK promoter. The chimeric gene was inserted into the TK locus of vaccinia virus. In the resulting recombinant vaccinia virus, vHBs5, there are 3 bp of extraneous DNA derived from the pUC9 multicloning region located immediately downstream from the

vaccinia TK promoter element. Additionally, the vaccinia TK promoter is separated from the translational start codon of the HBsAg gene by 127 bp of DNA derived from HBV. The DNA sequence separating the vaccinia TK promoter region and the HBsAg translational start codon is as follows. Restriction site is underlined.

BamHI

5′ GACGGATCCCAGAGTCAGGGGTCTGTATCTTCCTGCTGGTGGCTCCAGTTCAGGAAC
AGTAAACCCTGCTCCGAATATTGCCTCTCACATCTCGTCAATCTCCGCGAGGACTGGGGA
CCCTGTGACGAAC 3′

Thus, either "adjacency" is as in Venkatesan, and not described or enabled by Moss' examples and disclosure, or "adjacency" includes extraneous DNA, as exemplified in Moss (and therefore "adjacent" does not contain the exclusions called for by the Examiner); and therefore "adjacent" may only mean "purposeful placement" which is simply the same expression of the foreign gene under vaccinia control. In either case, Moss' claims lack novelty and are obvious.

MOSS' CLAIMS ARE ANTICIPATED OR OBVIOUS IN VIEW OF THE PRIOR ART

1. Moss Claims Lack Novelty

Moss claims 33, 41, 42, 43, 44, 52, 53, 54, 55 and 56 lack novelty over each of the '330 Patent, the Panicali PNAS

article, and the Panicali et al. Abstract (Exhibits 2 to 4). These documents each disclose plasmid pDP 137 which contains the gene coding for HSV TK inserted into the BamHI site of vaccinia in HindIII F in a right to left orientation, i.e., under the control of the F7L vaccinia promoter (see the '330 Patent, Fig. 3C and the Panicali PNAS article, page 4928, Fig. 1). That the HSV fragment contains DNA sequences which would act as a promoter in the context of an HSV infection is irrelevant to the expression of the HSV TK gene in the context of a recombinant poxvirus infection. This is so because by definition a promoter or "regulatory sequence" is DNA that functions in regulating the expression of a structural gene. If a DNA segment does not function in regulating the expression of a gene, it is not a regulatory sequence (see Exhibit 20, p. 408 of Dictionary of Biochemistry and Molecular Biology, (1989); see also USSN 072,455 at page 1, line 22 to page 2, line 5). Accordingly, plasmid pDP 137 can undergo homologous recombination (note vP2, vP4 and vP6) and comprises a chimeric gene which comprises at least one poxvirus transcriptional regulatory sequence (promoter) and, under the transcriptional control of the regulatory sequence (promoter), at least one uninterrupted protein coding sequence from a foreign gene, wherein the regulatory sequence or promoter and the coding sequence are "adjacent" or not separated by another transcriptional regulatory sequence or promoter. Plasmid pDP 137 also contains flanking DNA from the HindIII F region of

the vaccinia virus genome which is a non-essential region. Thus, the '330 Patent and the Panicali et al. PNAS article clearly disclose the subject matter of Moss claims 33, 41, 42, 44, 53, 55 and 56.

The Panicali et al. Abstract further discloses recombinant vaccinia viruses expressing the thymidine kinase gene from herpes simplex virus (HSV) or the hemagglutinin gene from influenza virus constructed by first inserting into a non-essential genetic locus of contiguous vaccinia virus DNA sequences cloned into plasmid pBR322. The donor chimeric plasmids were then introduced as calcium orthophosphate precipitates into eukaryotic tissue culture cells, previously infected with infectious virus.

The Panicali et al. Abstract continues by stating that expression was observed and that "[t]ranscriptional analysis of the HSV-TK gene was consistent with the utilization of endogenous vaccinia promoters" (lines 33 to 35). Additionally, the Panicali et al. Abstract states that "other foreign DNA sequences have been introduced into recombinant vaccinia viruses including segments of hepatitis B virus" (lines 36 to 39). The '330 Patent and the Panicali et al. PNAS article both teach that the foreign DNA can code for an antigen and VTK$^-$79, showing that the wild-type vaccinia virus TK region is non-essential; thereby the recitations of Moss claims 41 to 43 and 52 to 54 have been met.

The Panicali et al. Abstract further discloses a vector which can undergo homologous recombination in poxvirus comprising a chimeric gene which comprises at least one poxvirus transcriptional regulatory sequence ("utilization of endogenous vaccinia promoters") and under the transcriptional control of the regulatory sequence, at least one uninterrupted protein coding sequence from a foreign gene (HSV-TK, hemagglutinin gene from influenza virus, segments of hepatitis B virus) wherein the regulatory sequence and coding sequence are not separated by another promoter or transcriptional regulatory sequence ("utilization of endogenous vaccinia promoters") and DNA flanking the chimeric gene, from a non-essential region of poxvirus genome ("foreign gene was first inserted into a non-essential genetic locus of contiguous vaccinia virus DNA sequences cloned into pBR322" (lines 4 to 6)). That is, of the two possibilities, i.e., of whether certain HSV DNA acted as a promoter or whether a vaccinia promoter controlled expression, the Panicali et al. PNAS article clearly teaches and suggests that it is the vaccinia signals which are operative.

Moreover, in view of expression by vP2, vP4 and vP6 and not by vP1, vP3 and vP5, the '330 Patent discloses that "**the HSV TK-modified F-fragment is incorporated into the vaccinia variants** in the cell **and is then capable of** replication and **expression under vaccinia control**" (col. 10, lines 7 to 10; emphasis added). This is clearly a teaching that expression of the foreign gene in

the recombinant vaccinia virus (vP2, vP4 and vP6) was under the control of vaccinia (poxvirus) regulatory sequences. Also, the '330 patent teaches, at column 2, line 63 to column 3, line 1, "incorporation, into the mutant [i.e., in the exogenous DNA], of tandem repeats of the gene . . . or of additional genetic elements . . . or . . . the use of a strong promoter"; that is, the '330 Patent clearly teaches that the exogenous DNA can contain several genetic elements, including "a strong promoter". Thus, the '330 Patent clearly teaches a recombinant vaccinia virus wherein there is expression under vaccinia control and wherein the exogenous DNA can contain several genetic elements, including "a strong promoter", meaning a vaccinia promoter, since expression is taught as under vaccinia control.

The Panicali et al. PNAS article and the '330 Patent report that when the gene coding for the HSV TK is inserted into vaccinia virus at the BamHI site of vaccinia HindIII F in a right to left orientation (i.e., under the control of the F7L vaccinia promoter), functional HSV-TK enzyme is synthesized in these recombinants (vP2, vP4 and vP6) (see the Panicali et al. PNAS article, page 4929, left column).

The Panicali et al. article and the '330 Patent also report that when the gene encoding for the HSV TK is inserted into vaccinia virus at the BamHI site of vaccinia HindIII F in a left to right orientation (i.e., incorrect with respect to the F7L vaccinia promoter), functional HSV-TK enzyme is not detected

(vP1, vP3 and vP5) (see e.g., the Panicali et al. PNAS article discussion at page 4929, left column, lines 27 to 32 and page 4930).

Thus, the fact that the HSV fragment in the Panicali et al. PNAS article and the '330 Patent contains DNA sequences which would act as a promoter or a transcriptional regulatory sequences in the context of an HSV infection is irrelevant to the expression the HSV TK gene in the context of a recombinant poxvirus (vaccinia virus) infection.

Note additionally that the '330 Patent, in the further embodiment disclosed in column 15, lines 3 to 20 also recognizes that the endogenous promoter was operational (or that expression was under vaccinia control) and that there was not, as argued by Moss, reliance by Paoletti upon the presence of the HSV promoter. In that further embodiment, the HSV TK gene incorporated into the HindIII F-fragment of VTK⁻79 is, by recombination, "replaced by an F-fragment containing [another] exogenous gene."

The definition of "chimeric gene" in USSNs 07/072,455 and 06/445,451 (see Exhibit 9) is satisfied by several embodiments in the Panicali et al. Abstract, the Panicali PNAS article, and the '330 Patent, including the chimeric genes expressed in vP2 and vP6. The poxvirus transcriptional regulatory sequence which the Panicali PNAS article and the '330 Patent use in these examples is the F7L promoter, used in situ.

The complete promoter element is present, including the site at which RNA synthesis begins.

All of the examples in the Panicali et al. Abstract, the Panicali PNAS article, and the '330 Patent meet the definitions of "foreign gene" in USSN 06/445,451 and 07/072,455 (which definitions differ, see Exhibit 9) as the foreign genes inserted into vaccinia (HSV-TK, HSV gD, Influenza HA, HBsAg) include the translational initiation site (ATG) corresponding to the initiation of translation of the foreign gene (see e.g., the '330 Patent Fig. 3B).

Accordingly, the terms of the Moss claims 33, 41, 42, 43, 44, 52, 53, 54, 55 and 56 have been met by each of the Panicali et al. Abstract, the Panicali PNAS article, and the '330 Patent.[7]

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[7] As mentioned earlier, the Panicali et al. Abstract is in the prior art as to Moss, as is the Panicali et al. ASV presentation and the Paoletti laboratory CSH presentation. So that the APJ and the Board may have a full appreciation of the disclosure during those presentations, the non-confidential nature of their disclosure and, of the content of the prior art as to Moss, Exhibit 21 is a copy of Moss' European Patent, Virogenetics Corporation's Opposition Submission (including Weir et al., PNAS, 79: 1210-1214 (1982), Abstracts of the September 20-23, 1982 Workshop and Declaration of Marion Perkus) and the August 22, 1994 response by the Applicant/Proprietor of Moss' European Patent, and Exhibits 22 to 28 are respectively the Declaration of Drs. Samuel Dales, Anne-Marie Aubertin, James Tartaglia, Marion Perkus (Second Declaration), Dennis Hruby, Enzo Paoletti and Mr. Thomas J. Kowalski (with attachments), executed and to be filed in reply to the Applicant/Proprietor's response. Each of Virogenetics Corporation's Opposition submissions and the Declarations of Drs. Dales, Aubertin, Tartaglia, Perkus (Declaration and Second Declaration), Hruby and Paoletti, and of Mr. Kowalski, are hereby incorporated herein by reference. Each of the Dales, Aubertin, Tartaglia, Perkus, Hruby, Paoletti and Kowalski Declarations demonstrate the non-confidential nature of the Panicali et al. Abstract and of the Paoletti Laboratory CSH presentation; each of Hruby and Paoletti Declarations demonstrate the unpatentability of Moss claims and; the Paoletti Declaration demonstrates that the Panicali et al. ASV presentation disclosed the contents of the Panicali et al. PNAS article and the Panicali et al. Abstract. Thus, the APJ and Board are respectfully requested to consider the presentations and CSH abstracts as in the art and deem Moss' claims unpatentable in view thereof or, on the basis of the reasoning in the Hruby and Paoletti Declarations (consider also the admissions by Moss in Exhibits 6

2. Moss Claims Are Obvious

The subject matter of the Moss claims was certainly suggested by the '330 Patent, the Panicali et al. PNAS article, the Panicali et al. Abstract, the Panicali et al. ASV presentation or the Paoletti laboratory CSH presentation ("the primary references") either alone or in combination with other documents. Such other documents include the following secondary references: Weir et al. PNAS, 79: 1210-1214 (February 1982) ("Weir") (included in Exhibit 21), and/or Hruby and Ball, "Mapping and Identification of the Vaccinia Virus Thymidine Kinase Gene," J. Virol., 1982, 43:403-409 (August 1982) ("Hruby 1982"; copy attached to Exhibits 26 and 27) and/or Venkatesan et al., Cell 125:805-813, September 1981 (Exhibit 1) and/or Venkatesan et al. September 20-23, 1982 Workshop Abstract at page 40 ("Abstract 40"; Exhibit 21) and/or Weir et al. September 20-23, 1982 Workshop Abstract at page 59 ("Abstract 59"; Exhibit 21) alone, or together with the tertiary references: Molecular Biology of the Gene, p. 714 (3d Ed. by James Watson, 1976) (a standard textbook), and Pribnow, "Genetic Control Signals in DNA", ch. 7 in Volume 1, "Gene Expression" of Biological Regulation and Development (edited by Robert F. Goldbeyer) ("Pribnow"), 1980, especially Sections 2.1, "The Transcript Unit", and 3.1, "The Promoter", p. 230, 231, optionally in

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and 7 hereto).

further view of at least one of Rosenberg and Court (1979), "Regulatory sequences involved in the promotion and termination of RNA transcription," Ann. Rev. Genetics 13:319-353 and Breathnach and Chambon (1981), "Organization and expression of eucaryotic split genes coding for proteins", Ann. Rev. Biochem.50:349-383.[8]

A. The Primary References

Each of the Panicali et al. PNAS article, the '330 Patent, the Panicali et al. Abstract, the Panicali et al. ASV presentation and, the Paoletti laboratory CSH presentation disclosed the construction of six vaccinia virus HSV TK recombinants and the expression by three of those recombinants. More specifically, these documents and presentations and especially the Panicali et al. PNAS article and the '330 Patent disclose vP1 to vP6. vP1, vP3 and vP5 were derived from pDP132

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[8] For convenient reference, a copy of each of Molecular Biology of the Gene, p. 714, Pribnow, Rosenberg and Court, and Breathnach and Chambon, is attached to Exhibits 26 and 27. Also, in this regard (and as tertiary references), mention is made of Moss et al., "Deletion of a 9,000-Base-Pair Segment of the Vaccinia Virus Genome that Encodes Nonessential Polypeptides", J. Virol., 1981, 40: 387-95 (believed of record and available in Moss applications; "Moss et al. 1981"), Panicali et al., "Two Major DNA Variants ...", J. Virol., 1981, 37:1000-1010 (copy attached to Exhibits 26 and 27; "Panicali et al. 1981") and Hruby et al., J. Virol., 1981, 40:456-64 (copy attached to Exhibits 26 and 27; "Hruby 1981"), which can be read with the '330 Patent, the Panicali et al. PNAS article, the Panicali et al. Abstract, the Panicali et al. ASV conference or the Paoletti Laboratory CSH presentation, alone or collectively and/or with any of the other documents above-cited.

and vP2, vP4 and vP6 were derived from pDP137. The direction of the Bam HSV TK fragment in each of pDP132 and pDP137 were opposite to the other, to thereby obtain expression in a set of recombinants, regardless of whether expression is under the control of HSV DNA acting as a promoter or a vaccinia promoter and, to ascertain logically which of these indeed controlled expression.

vP2, vP4 and vP6 all expressed the HSV TK gene, whereas vP1, vP3 and vP5 did not, because of the orientation of the gene in these recombinants. **The Panicali et al. article at page 4931 clearly states: "[T]hat vaccinia signals may be operative for HSV TK expression" in vP2, vP4 and vP6. That is, of the two possibilities, i.e., whether certain HSV DNA acted as a promoter or whether a vaccinia promoter controlled expression, the Panicali et al. article clearly teaches and suggests that it is the vaccinia signals which are operative.**

Moreover, in view of expression by vP2, vP4 and vP6 and not by vP1, vP3 and vP5, the '330 Patent discloses that "**the HSV TK-modified F-fragment is incorporated into the vaccinia variants** in the cell **and is then capable of** replication and **expression under vaccinia control**" (col. 10, lines 7 to 10; emphasis added). This is clearly a teaching that expression of the foreign gene in the recombinant vaccinia virus (vP2, vP4 and vP6) was by vaccinia (poxvirus) regulatory sequences (control) (see also col. 15, lines 3 to 20; further embodiment without HSV TK). Also, the

'330 Patent teaches at column 2, line 63 to column 3, line 1, "incorporation, into the mutant [i.e., in the exogenous DNA], of tandem repeats of the gene . . . or of additional genetic elements . . . or . . . the use of a strong promoter"; that is, the '330 Patent clearly teaches that the exogenous DNA can contain several genetic elements, including "a strong promoter". Thus, the '330 Patent clearly teaches a recombinant vaccinia virus wherein there is expression under vaccinia control (promoter) and, wherein the exogenous DNA can contain several genetic elements, including "a strong promoter."

The Panicali et al. Abstract entitled "Poxvirus As Eukaryotic Cloning Vectors," reads (with emphasis added):

> Recombinant vaccinia viruses expressing the thymidine kinase gene from Herpes simplex virus (HSV) or the hemagglutinin gene from influenza virus have been constructed and characterized. The foreign gene was first inserted into a non-essential genetic locus of contiguous vaccinia virus DNA sequences cloned in pBR322. These donor chimeric plasmids were introduced as calcium orthophosphate precipitates into eukaryotic tissue culture cell, previously infected with infectious virus. Site specific in vitro recombination allowed incorporation of the foreign DNA into the genome of replicating virus. Progeny virus containing the foreign gene were obtained as purified populations by several procedures.
>
> The HSV-TK was incorporated into both the 120 Md prototypic L variant genome, as well as into the S variant, a spontaneous deletion mutant. When rescuing virus was TK^- recombinants expressing HSV-TK were selected on TK cells in the presence of methotrexate. When rescuing virus was TK+, recombinant

> vaccinia viruses expressing HSV-TK were detected by the specific utilization of 125I-deoxycytidine (IDC). The endogenous vaccinia TK as well as the TK from a variety of eukaryotic cells failed to utilize IDC as substrate. Recombinant vaccinia viruses containing foreign genetic elements were additionally selected by a novel replica filter plating technique developed in our laboratory. This methodology is independent of expression or biochemical selectability of the foreign gene product and provides a general and rapid procedure for detection and recovery of viral vectors containing foreign genetic elements.
>
> Restriction analysis of progeny recombinant viral DNA demonstrated the insertion and stable integration as a very specific event. Transcriptional analysis of the HSV-TK gene was consistent with the utilization of endogenous vaccinia promoters.
>
> In addition to the foreign genes described above, other foreign DNA sequences have been introduced into recombinant vaccinia virus including segments of Hepatitis B virus. As much as 20 Kbp of foreign DNA have been stably inserted into recombinant vaccinia viruses as an attempt to determine the upper limit of foreign DNA packaging by the virus.

In Exhibits 22, 25 and 27, Drs. Perkus and Paoletti confirm that contents of the Panicali et al. PNAS article and Panicali et al. Abstract were disclosed in the Panicali et al. ASV presentation and the Paoletti laboratory CSH presentation. Indeed, in paragraph 7 of Exhibit 27, Dr. Paoletti states:

> The Panicali et al. ASV presentation included contents of the Panicali et al. PNAS article, the Panicali et al. Abstract and of the Paoletti laboratory CSH presentation. In particular, the Panicali et al. PNAS article, at page 4931 states that: "other (unpublished) data suggest that vaccinia

> signals may be operative for HSV TK expression [in recombinants vP2, vP4 and vP6]." The Panicali et al. Abstract disclosed that "transcriptional analysis . . . was consistent with endogenous vaccinia promoters." The Paoletti laboratory CSH presentation and the Panicali et al. ASV presentation both detailed the use of recombinant vaccinia virus to express foreign gene products and, that vaccinia promoter was operative in that expression. Indeed, I do not recall any significant differences in content between the Panicali et al. ASV presentation and the Paoletti laboratory CSH presentation. That is, in the Panicali et al. PNAS article, the Panicali et al. ASV presentation, the Panicali et al. Abstract and, the Paoletti laboratory CSH presentation, expression in recombinant vaccinia virus by operation or use of a vaccinia promoter or, expression in recombinant vaccinia virus of exogenous DNA under vaccinia control, was fully disclosed; and, the Panicali et al. PNAS article, the Panicali et al. ASV presentation and, the Panicali et al. Abstract were all unquestionably publicly disseminated before the September 20, 1982 meeting of the September 20-23, 1982 Workshop.

B. The Secondary and Tertiary References

As shown in Pribnow, Section 2.1 at p. 230 (Exhibits 26 and 27) a "transcriptional unit is a stretch of DNA base pairs bounded on one end by a 'start sequence' or *promoter* . . . and the other end by a 'stop sequence' or *terminator*" (emphasis in original). Moss, in the European Opposition, admits that

> D1 [Venkatesan et al., Cell 125 805-813 September 1981] discusses the 5' region containing the RNA start site of the vaccinia gene encoding a 7.5 Kd polypeptide . . . Sequences corresponding to this region were later used to obtain the vaccinia 7.5 K promoter.

The "5' region containing the RNA start site of the vaccinia gene encoding a 7.5 Kd polypeptide" is "the vaccinia 7.5 K promoter". Thus, the sequence of the 7.5 K promoter was disclosed in Venkatesan (Exhibit 1). No further information other than the information disclosed in Venkatesan (Exhibit 1) was required to "obtain the vaccinia 7.5 K promoter". Accordingly, the Panicali et al. PNAS article or the '330 Patent, or the Panicali et al. Abstract, or the Panicali et al. ASV presentation, or the Paoletti laboratory CSH presentation ("the primary references") either alone or in view of Venkatesan (Exhibit 1) render obvious the claims of the Moss application especially in view of the following detailed discussion of the state of the art.

A standard textbook published in 1976 defines a promoter as a "[r]egion on DNA at which RNA polymerase binds and initiates transcription" (p. 714, Molecular Biology of the Gene, 3rd edition, by James Watson). Similarly, in 1980 David Pribnow stated "The basic promoter is only that particular DNA sequence that is recognized directly and used by the RNA polymerase as a start signal for transcription" (Pribnow 1980, section 3.1 "The Promoter", p. 231).

The nature of and elements contained within both procaryotic and eucaryotic promoters were well defined before the filing date of the Moss application. (Rosenberg and Court, 1979; Pribnow 1980; Breathnach and Chambon, 1981). In particular, it

was well established that promoters are commonly located upstream from the ATG initiation of translation sites which begin DNA sequences coding for proteins. In Venkatesan (Exhibit 1), the authors demonstrate extensive familiarity with this knowledge in the state of the art by citing and discussing several publications which reveal elements and characteristics of various procaryotic and eucaryotic promoters (Rosenberg and Court, 1979; Pribnow 1980; Benoist et al., 1980; Flavell et al., 1979; Canaani et al., 1979; Baker et al., 1979; Hashimoto and Green, 1980). The authors of Venkatesan (Exhibit 1) also discuss the occurrence of sequence motifs near the potential AUG initiation of translation sites in the 7.5 K mRNA which are similar to sequence motifs found near the initiation of translation codons found in various other virus RNAs (vesicular stomatitis virus RNA, alfalfa mosaic virus RNA 4: Rose 1978; late adenovirus mRNA: Ziff and Evans, 1978; turnip yellow mosaic virus mRNA: Briand et al., 1978).

In its title (p. 805) Venkatesan (Exhibit 1) disclosed, "distinctive nucleotide sequence adjacent to multiple initiation . . . sites of an early vaccinia virus gene" (i.e., the 7.5 Kd gene; emphasis added). The summary of Venkatesan (Exhibit 1) (p. 805) includes the following:

> A remarkable 88% AT-rich 60 bp DNA sequence was found immediately upstream of the initiation of transcription sites. Although DNA sequences that bear some homology to Pribnow and Hogness boxes are present, additional recognition sequences located further upstream of

> procaryotic and eucaryotic initiation sites are absent. A possible initiation of translation codon occurs about 50 nucelotides from the 5′ end of the message.

The preceding quotation clearly describes sequence characteristics of the 7.5 Kd promoter, in comparison to the sequences of canonical procaryotic promoters (which contain a Pribnow box) and eucaryotic promoters (which contain a Hogness box). As the authors in Venkatesan (Exhibit 1) note (p. 810).

> AT-rich sequences previously have been found within the promoter regions of procaryotic and eucaryotic mRNAs AT-rich region near the viral initiation of transcription site showed some homology to similar regions of procaryotic and eucaryotic genomes, additional homology was not found further upstream.

In Venkatesan (Exhibit 1) the authors further note (p. 805), col. 1. lines 7-14) that

> Recently several mRNAs made early after vaccinia virus infection ... and in vitro by virus cores (Venkatesan and Moss, 1981) have been mapped on the vaccinia virus genome. These early mRNAs are not spliced and their cap structures retain the β-^{32}P-label of the initiating nucleotide, indicating the absence of processing at the 5′-end.

As the authors of Venkatesan (Exhibit 1) stress (p. 809), referring to the mRNA for the 7.5 Kd polypeptide,

> the β-phosphate of GTP previously was shown to be incorporated into cap structures of this mRNA, providing evidence of the strongest kind that the 5′ ends represent true initiation sites (Venkatesan and Moss, 1981)

(i.e., that the 5′ end of the mRNA maps to the 7.5 K promoter region).

Finally, (at p. 811) the authors of Venkatesan (Exhibit 1) conclude

> The multisubunit RNA polymerase of vaccinia virus, like that of procaryotic and eucaryotic organisms, must be capable of interacting with the promoter sequences for a large number of RNAs. Efforts to extend the present studies by sequencing additional genes are in progress.

It is thus evident that the DNA sequences disclosed in Venkatesan (Exhibit 1) around the 5′ end of the mRNA for the 7.5 polypeptide are in fact, and were at the time of publication thereof known to be, the promoter sequences for the 7.5 K gene (note also the Moss admissions in Exhibit 6 and 7).

With respect to Weir (Exhibit 21), since this article discloses that "the vaccinia thymidine kinase gene maps to the 5,000 bp *Hin*dIII J fragment", the "person of skill in the art", who wished to obtain a vaccinia TK promoter would naturally focus his search to sequences within the vaccinia *Hin*dIII J fragment. The "person of skill in the art" would expect that the TK promoter would be located in "upstream sequences of the TK gene". In Weir (Exhibit 21), the authors acknowledge that they are not the only group that had mapped the TK gene to *Hin*dIII J (p. 1210, col. 2, lines 30-34): "Further evidence that the *Hin*dIII J fragment contains the structural TK gene was obtained in our laboratory and in that of D.E. Hruby and L.A. Ball (personal communication) by cell-free translation of hybridization selected mRNA under conditions suitable for expression of active TK."

Prior to November 30, 1982, Drs. Ball and Hruby, in Hruby 1982 (Exhibits 26 and 27), reported in detail the location of the vaccinia TK gene. Hruby 1982 reports that the vaccinia TK gene was transcribed as a 700 nt RNA, and that, contrary to previous expectations, the gene encoded a 19 kilodalton protein. Hruby 1982 reported that "the tk gene lies completely within *Hin*dIII fragment J, and this conclusion is supported by recent analyses of subfragments of J, which show that the gene lies between about 0.5 and 1.2 kilobases from the L-J boundary". Hruby 1982 also disclosed that "the structural gene for VVtk is located in *Hin*dIII fragment J at 42.5 to 45.1 map units".

Thus, prior to the Moss application, information was available in the public domain which could be used by persons "of skill in the art" to obtain the vaccinia TK promoter, without any inventive efforts. Note also Hruby 1981, and the Moss admissions in Exhibits 6 and 7. See also Moss et al. 1981 and Panicali 1981, which, like the Moss admissions in Exhibits 6 and 7, show that the vaccinia genome was known to contain numerous promoters. For instance, in one region of the vaccinia genome Moss et al. 1981 confirmed that it was "an immediate early or early transcriptional unit [which] ... encodes a minimum of seven or eight immediate early ... polypeptides." Note again the '330 Patent's teaching that the exogenous DNA can contain several genetic elements, including "a strong promoter" (i.e., a vaccinia

promoter, since the '330 Patent teaches expression under vaccinia control).

Abstract 40, entitled, "Nucleotide Sequences of Five Vaccinia Virus Early Genes", states in part:

> An unusually A·T-rich sequence has been found before a vaccinia virus gene specifying an early 7.5 K polypeptide (Venkatesan, Baroudy and Moss, Cell 125, 805, 1981). . . . [W]e have now sequenced five additional early genes. Three of the sequenced genes are located within the 10,000 bp inverted terminal repetition and were found to encode early mRNAs of about 1,000, 600, and 1,050 nucleotides that directed in vitro synthesis of 7.5 K, 19K and 42K polypeptides respectively. . . . The sixth gene specifies thymidine kinase and will be presented separately. Previous studies established that none of these mRNAs are spliced and in several cases, the capped ends were shown to be sites of transcriptional initiations. . . . Common features of the early genes include extremely A·T-rich 40 to 60 bp segments immediately upstream of the transcriptional initiation sites, uninterrupted coding sequences, absence of eukaryotic poly(A) signal sequence, and multiple closely spaced 5′ and 3′ ends of transcripts. Distances between transcriptional and translational initiation sites and translational and transcriptional termination sites were quite variable. In some cases, genes were closely spaced with as little as 10 bp between the end of one and the start of another suggesting overlapping of regulatory sequences for initiation and termination of transcription.

Thus, the transcriptional regulatory sequence which regulates the early vaccinia virus gene encoding the 7.5 K polypeptide was well-known and part of the art, prior to the alleged November 30, 1982 filing date of Moss.

Abstract 59, entitled, "Identification and Nucleotide Sequence of the Thymidine Kinase Gene of Wild-type Vaccinia Virus and Nonsense Mutants", states:

> The thymidine kinase (TK) gene has been mapped within the HindIII J fragment of vaccinia virus DNA (Weir, Bajszar and Moss, Proc. Natl. Acad. Sci. USA, 79, 1210, 1982). Further investigations revealed that enzymatically active TK was made in reticulocyte lysates programmed with early vaccinia mRNA that hybridized to plasmid recombinants containing either of two adjacent small DNA subsegments of the viral HindIII J fragment. The map position of an early polypeptide, with a molecular weight of about 19,000 (19K), coincide precisely with that of the TK. The absence of the 19K polypeptide in cell-free translation products of hybridization-selected mRNAs from several TK^- mutants provided an independent identification of the TK polypeptide. The small size of the TK polypeptide of the vaccinia virus distinguishes it from that of prokaryotes, eukaryotes and herpesvirus. RNAs of 590 and 2,380 nucleotides with 5′ coterminal ends represent major and minor forms, respectively, of the TK message. The TK genes of wild-type and 3 putative nonsense mutants were cloned and sequenced by the dideoxynucleotide chain termination method. In each of the mutant DNAs, an extra nucleotide identical to one preceding it had been added. Because of the framshift, a nonsense codon was introduced downstream. The region preceding the transcriptional initiation site of the TK gene is AT-rich and shares some sequence homology with similar regions of other early genes. Interestingly, the putative transcriptional regulatory region of the TK gene lies within the coding sequence of an adjacent late gene. Moreover, the 3′ end of the late transcript overlaps the TK genes.

Thus, before the alleged filing date of Moss, flanking DNA comprising the vaccinia virus thymidine kinase gene, as well as the transcriptional regulatory sequence which regulates the vaccinia virus thymidine kinase gene, were known in the art.

Thus, the primary and secondary references, either alone or with the tertiary references, placed into the knowledge of the skilled artisan:

- recombinant vaccinia virus;
- with expression of exogenous DNA therein under vaccinia control;
- with exogenous DNA therein deliberately placed proximal to vaccinia promoters;
- the 7.5 K promoter;
- that the 7.5 K promoter naturally occurs adjacent to the coding sequence for the 7.5 K polypeptide; and,
- the mapping and identification of the vaccinia virus thymidine kinase gene.

Accordingly, without inventive effort, one skilled in the art: could place desired exogenous DNA proximal to a vaccinia promoter; could place a desired promoter, such as the 7.5 K promoter, adjacent to coding DNA, as such occurs naturally with respect to the 7.5 K promoter and coding sequence for the 7.5 K polypeptide; and, could locate the vaccinia virus TK promoter by looking to sequences upstream from the mapped and identified gene therefor, since promoters for other vaccinia

virus genes, such as for the 7.5 K polypeptide, were known to be adjacent to and upstream from the gene.

From the literature, it is clear that deliberately employing or purposefully placing poxvirus (vaccinia) transcriptional regulatory sequences (promoters) to control expression of the foreign gene such as by inserting the poxvirus (vaccine) regulatory sequence or promoter into the poxvirus along with the foreign gene was within the ambit of the skilled artisan (particularly considering that expression under vaccinia control and expression by endogenous vaccinia promoter was in the art) and, was a simple duplication of that which had already been disclosed, particularly as naturally occurring with respect to the 7.5 K polypeptide gene and the promoter therefor. The exogenous DNA in the primary references was expressed under vaccinia control and was not fortuitously-proximal to a vaccinia virus promoter as asserted by Moss.

Therefore, each and every recitation of each and every one of Moss claims 33, 36, 37, 39, 41, 42, 43, 44, 47, 48, 50, 52, 53, 54, 55, 56 and 57 by any of the primary references and any of the secondary references, alone or in further view of any of the tertiary references is obvious. This analysis of the art is confirmed the by Hruby and Paoletti Declarations, attached as Exhibits 26 and 27.

3. The Obviousness of Moss' Methodology

In 1982 the use of promoter elements for expression of heterologous genes using defined, translocated promoter elements, was not inventive. In particular, as confirmed in Exhibit 27, the Declaration of Dr. Paoletti:

A. Prokaryotic Vectors

The technology of expressing heterologous genes in prokaryotes, specifically in *E. coli*, through the use of translocated promoter elements was well established prior to 1982. In particular, a number of research groups had demonstrated the expression of eukaryotic genes in *E. coli* through the use of translocated prokaryotic promoter elements. Several examples are described below.

(1) In 1980, Guarente, et al. published "A technique for expressing eukaryotic genes in bacteria," Science 209:1428-1430 (copy attached to Exhibit 27). In their technique, they insert a small PvuII/PstI "portable promoter fragment" containing the *E. coli lac Z* promoter.

(2) Kupper et al. (1981), "Cloning of cDNA of major antigen of foot and mouth disease virus and expression in *E. coli*," Nature 289:555-559 (copy attached to Exhibit 27), used a small restriction fragment containing the P_L promoter from *E. coli* bacteriophage λ in a plasmid background to direct the expression of the major antigen of foot and mouth disease virus (FMDV).

(3) In October 1982, Watson et al. (1982), "Herpes simplex virus Type-1 glycoprotein D gene: nucleotide sequence and expression in *Escherichia coli*," Science 218:381-384 (copy attached to Exhibit 27) used a "modified λ cro sequence" in a plasmid as a promoter to direct the expression of the HSV-1 glycoprotein D gene in *E. coli*.

(4) Kleid et al. (1981), "Cloned viral protein vaccine for foot-and-mouth disease: responses in cattle and swine," Science 214: 1125-1129 (copy attached to Exhibit 27), reported the use of small, translocated fragments containing the promoter from the *E. coli* trp (tryptophan) operon ("trp-operon") to express FMDV vP_3 in *E. coli*.

(5) Edman et al. (1981), "Synthesis of hepatitis B surface and core antigens in *E. coli*," Nature 291:503-506 (copy attached to Exhibit 27) disclosed the use of small translocated fragments containing the promoter from the *E. coli* trp-operon for expression of the hepatitis B core antigen in *E. coli*.

(6) Emtage et al. (1980), "Influenza antigenic determinants are expressed from haemagglutinin genes cloned in *Escherichia coli*," Nature 283:171-174 (copy attached to Exhibit 27), disclosed the use of small, translocated fragments containing the promoter from the *E. coli* trp-operon to express influenza HA in *E. Coli*.

B. Eukaryotic Vectors

An understanding of the state of the art in 1982 of expressing heterologous eukaryotic genes in eukaryotic cells through the use of translocated eukaryotic promoter elements can be obtained by referring to the book Gluzman, Y. ed. (1982) "*Eukaryotic Viral Vectors*", Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, containing the following, a copy of each of which is attached to Exhibit 27:

Berkner, K.L. and P.A. Sharp, "Preparation of adenovirus recombinants using plasmids of viral DNA," pp. 193-198.

Fried, M. and E. Ruley, "Use of polyoma virus vector," pp. 67-70.

Gilboa et al. "Transduction and expression of nonselectable genes using retrovirus-derived vectors," pp. 145-151.

Gluzman, Y. Preface pp. xI-xII.

Hassell et al. "The construction of polyoma virus vectors: functions required for gene expression," pp. 71-77.

Liu, C.C. and A.D. Levinson, "Expression of hepatitis B surface antigen using lytic and nonlytic SV40-based vectors," pp. 55-60.

Southern, P. and P. Berg, "Mammalian cell transformation with SV40 vector, "pp. 41-45

The preface to the book, by Yakov Gluzman, of Cold Spring Harbor Laboratory, begins as follows:

> A conference on eukaryotic viral vectors was held at the Banbury Center of the Cold Spring Harbor Laboratory December 3-6, 1981. Approximately 40 DNA and RNA tumor virologists presented and discussed the most recent advances in the use of tumor viruses as cloning vectors.
>
> Progress in this field can be judged by comparing this conference with last year's Banbury meeting on Construction and Use of Mammalian Vectors (December 1980). One year ago, the only viral vectors constructed and used were from SV40 and adenovirus; papilloma and RNA tumor viruses were merely discussed as potential vectors. In contrast, during this meeting, work with a great variety of vectors, including both DNA tumor viruses (SV40, polyoma, papilloma, adenoviruses, herpesvirus) and RNA tumor viruses (MoMLV, MoMSV, HaMSV, ASV, SNV, MMTV), was presented. *Eukaryotic Viral Vectors* summarizes the results of this conference in the form of extended abstracts provided by the speakers. These abstracts are intended to provide the interested reader with an overview of current work in this rapidly progressing field.

Several examples of relevant abstracts published in *Eukaryotic Viral Vectors* are described below.

(1) Two abstracts specifically refer to the movement of small fragments of DNA containing SV40 promoters and other regulatory signals to bacterial plasmids in order to direct the transcription of foreign genes in eukaryotic cells.

> A series of hybrid plasmid vectors has been developed that can be maintained in both bacterial and mammalian cells. . . . The vectors include sequences from the plasmid pBR322 that permit selection and propagation

> in *Escherichia coli*. The vectors also contain segments of the SV40 genome that constitute a defined eukaryotic transcription unit - promoter, intervening sequence, and polyadenylation site. Foreign DNA sequences (cDNAs or bacterial genes) are inserted adjacent to the SV40 early promoter . . . (Southern and Berg, p. 41).

The legend to Figure 1 of Southern and Berg describes the "structure of the pSV-*neo* hybrid plasmids" which are designed to express the bacterial neomycin resistance gene (the *neo* gene) under the control of the SV40 early promoter. The physical form and location of the promoter are defined:

> The SV40 origin of replication (SV40 ori) and the SV40 early promoter are present on a small fragment (SV40 map units 0.71-0.65) immediately 5′ to the *neo* gene (Southern and Berg, p. 43).

(2) Similarly, in another abstract, Liu and Levinson state:

> Since plasmids containing sequences derived from pBR322 and SV40 are capable of replicating in cells in the presence of SV40 T antigen. . . . we sought to utilize and extend this system so that foreign gene inserts could be efficiently expressed. . . . Two fragments of SV40 that span the origin were used. One was 311-bp fragment generated by *EcoRI* digestion of SV40 DNA. . . . The other was a 348-bp fragment resulting from digestion with both *PvuII* and *HindIII*. . . . Because the origin region of SV40 encodes the promoters for both the early and late viral transcription units (in opposite orientations), we utilized these fragments in concert with the sequences encoding HBsAg to evaluate their function. Our results indicate that the SV40 promoter, in either the early or late orientation, is capable of efficiently directing the

> transcription of distal heterologous genes. (Liu and Levinson, pp. 57-58)

Thus, the technology, through the use of restriction endonucleases, of isolating a small restriction fragment containing a promoter from its native location in a particular genome, inserting the fragment in another genetic environment, and using the promoter contained therein to direct the expression of a heterologous gene, was in the state of the art before November 1982.

(3) Fried and Ruley describe the addition of polyoma virus DNA sequences including the polyoma early promoter into bacterial plasmid pAT153, thus creating a "polyoma virus vector". They describe the use of this hybrid vector to express HSV-TK:

> The herpes 2.4-kb *Eco*RI fragment contains the structural gene for herpes TK but is lacking 5′ control sequences necessary for efficient expression of the gene. This *Eco*RI fragment cloned into the *Eco*RI site of plasmid pAT153 is 20-100 fold inhibited in comparison with the herpes tk 3.6-kb BamHI fragment (cloned in the BamHI site) in converting Ltk-cells to a tk+ phenotype. When the *Eco*RI tk fragment is inserted into the polyoma virus vector at the *Eco*RI site, tk activity is restored (5-25 tk+ colonies/ng of tk gene). Activity is restored only when polyoma control sequences are attached to the 5′ end of the *Eco*RI tk fragment so that polyoma transcription is in the same orientation as the tk gene. (Fried and Ruley, pp. 68-69).

Using their "polyoma virus vector", the authors also demonstrate expression of "the structural gene for human fibroblast interferon . . . under polyoma virus control" (p. 69).

(4) Hassell and co-worker describe the "construction of a polyoma virus pBR322 vector suitable for the molecular cloning and characterization of mammalian promoters". As a test of their system, they describe the insertion of SV40 promoters into the hybrid vector and assay for their ability to direct the expression of the polyoma viral oncogene:

> Evidence that foreign promoters can be used to direct expression of the viral oncogene was provided by inserting a fragment of SV40 DNA (the *Hind*III to C fragment) bearing its early and late promoters, upstream of the polyoma viral oncogene. . . . The resulting recombinant plasmids contain either the SV40 early (pSVE1) or late (pSVL1) promoter proximal to the polyoma viral oncogene. . . . As shown in Table 3, the SV40 early promoter completely restored transforming activity. (Hassell et al., p. 75).

This provides a further example wherein a small restriction fragment containing a promoter can be translocated from its native location in a particular genome and inserted into another genetic environment, where it can function as a promoter to direct the expression of a heterologous gene. In another example, the same authors further report that "preliminary experiments reveal that the major late adenovirus type-2 (Ad2) promoter, when properly juxtaposed before the polyoma viral

oncogene, will elicit expression of downstream sequences" (p. 76).

(5) In the process of constructing retrovirus-derived vectors, Gilboa and co-workers describe how they "have identified functionally and isolated physically two viral DNA fragments carrying the *cis*-acting functions required for the expression of the Mo-MLV genes" (Gilboa et al., p. 148) They identified the two Mo-MLV promoters by cloning small fragments of Mo-MLV DNA upstream from HSV-TK coding sequences in a pBR322 background, then testing the resulting plasmids for tk expression by transfection of the tk- mouse cells in the presence of HAT selection (which selects for tk activity). In this example also, a translocated promoter element was shown to be functional for the expression of a heterologous gene.

(6) Berkner and Sharp present data on "preparation of adenovirus recombinants using plasmids of viral DNA." They describe the construction of an adenovirus recombinant that contains the positive selection marker dihydrofolate reductase (DHFR) under the control of the adenovirus late promoter. The authors suggest that, with their construct, "subsequent manipulation of the adenoviral late promoter, or even replacement by other putative strong promoters, can be readily evaluated" (Berkner and Sharp, p. 198) Thus, the concepts and techniques of *in vitro* manipulation of promoters and

experimental interchange of different promoters were clearly in the state of the art before November 1982.

(7) A number of studies published prior to November 1982 from the laboratory of Bernard Roizman detail progress in analyzing moveable promoter elements using herpes simplex virus. In some of these studies, the authors inserted a moveable promoter element upstream from HSV-TK coding sequences, then monitored expression of the HSV-TK gene (Note Moss' citation to work of Roizman and Post in Exhibit 7). Using this technique, they demonstrated in 1981 that HSV-TK, which is normally regulated as a β gene, can be expressed as an α gene when placed under the control of a Herpes α promoter derived from the upstream region of the HSV α ICP 4 gene (Post et al. (1981), "Regulation of α genes of herpes simplex virus: expression of chimeric genes produced by fusion of thymidine kinase with α gene promoters," Cell 24:555-565; copy attached to Exhibit 27). In the same publication they demonstrated that the chimeric gene composed of TK coding sequences fused to the α promoter unit could be inserted into the HSV genome, generating a recombinant herpes virus wherein the TK is transcribed under the control of the α promoter. They also demonstrate that the chimeric gene composed of TK coding sequences fused to the α promoter unit could be used to convert LtK- cells to tk+ phenotype. Upon infection of the cell with HSV, the TK coding sequences in the

chimeric gene is transcribed under the control of the α promoter, and is regulated as an α gene.

(8) In August 1982, members of the Roizman group reported that a transposed DNA fragment extending 110 nucleotides upstream from the start of RNA transcription for the α ICP 4 gene is sufficient to direct the expression of the TK coding sequences in a chimeric gene, and that a larger DNA fragment, extending beyond 110 nucleotides upstream from the start of RNA transcription, is capable of directing the expression of the chimeric TK gene as an inducible α gene (Mackem, S. and B. Roizman (1982), "Differentiation between α promoter and regulator regions of herpes simplex virus 1: the functional domains and sequence of a movable α regulator," Proc. Natl. Acad. Sci. USA 79:4917-4921, (copy attached to Exhibit 27). In September 1982, the same authors reported that a 325 nucleotide moveable promoter fragment from another HSV α gene, the α gene no. 27, when placed upstream from the HSV-TK coding sequences, was sufficient to specify expression of TK under α regulation (Mackem, S. and B. Roizman (1982), "Regulation of α genes of herpes simplex virus: the α 27 gene promoter-thymidine kinase chimera is positively regulated in converted L cells," J. Virol. 43:1015-1023, copy attached to Exhibit 27).

(9) In March 1982, members of the Roizman group described a plasmid system designed to introduce foreign genes into cells. Plasmid vectors were constructed which contain the

HSV-TK gene as a selectable marker, along with coding sequences for the foreign gene placed under the control of a translocated copy of the HSV α 4 promoter. In this technique, Ltk- cells are transfected with the plasmid, then cell lines are selected for conversion to the tk+ phenotype. As an example of this technique, Post et al. demonstrated expression of the chicken ovalbumin gene in transfected cells under the control of the translocated HSV α 4 promoter element (Post et al. (1982), "Chicken ovalbumin gene fused to a herpes simplex virus α promoter and linked to a thymidine kinase gene is regulated like a viral gene," Mol. Cell. Biol. 2:233-240, copy attached to Exhibit 27).

C. Vaccinia Virus

In view of the foregoing discussion of the state of the art in 1982 pertaining to the use of promoter elements for expression of heterologous genes using defined, translocated promoter elements, with reference to other eukaryotic and prokaryotic vectors, the methodology of Moss, namely of having the DNA inserted into vaccinia virus containing both a vaccinia promoter for expression and the exogenous gene to be expressed, is neither novel nor nonobvious; but rather, is the anticipated and obvious extension of the art of the other eukaryotic and prokaryotic vectors to vaccinia virus, especially in view of the disclosure in any of the '330 Patent, the Panicali et al. PNAS article, the Panicali et al. Abstract, the Panicali et al. ASV

presentation and the Paoletti laboratory CSH presentation (recombinant vaccinia virus with expression of exogenous DNA by use of vaccinia promoter) alone, or, in further view of any of Venkatesan (Exhibit 1) (disclosure of "distinctive nucleotide sequence [i.e., the 7.5 Kd promoter] adjacent to multiple initiation. . . . sites of an early vaccinia virus gene", i.e., the 7.5 Kd gene; emphasis added) and either or both of Weir (Exhibit 21) or Hruby 1982 (Exhibits 26 and 27) (disclosure of location of vaccinia TK gene from which one skilled in the art could isolate the TK promoter without any inventive effort). Note again the above discussion of each of the '330 Patent, the Panicali et al. Abstract, the Panicali et al. ASV presentation, the Paoletti laboratory CSH presentation, Venkatesan, Weir and Hruby 1982. Note particularly that the '330 Patent allows for the DNA insert to include "a strong promoter" (which must be a vaccinia promoter in view of the '330 Patent also teaching expression under vaccinia control) and, that Venkatesan, Weir and Hruby 1982 clearly teach enough for the skilled artisan to isolate the vaccinia 7.5 Kd and TK promoters; and, that Venkatesan when read in the light of the state of the art before November 1982 taught that in vaccinia virus promoters are naturally "adjacent to" the gene to be expressed (see also the admissions of Moss in Exhibits 6 and 7).

Thus, the Moss methodology is not novel or nonobvious; but rather, is merely a following or a confirmation or an obvious

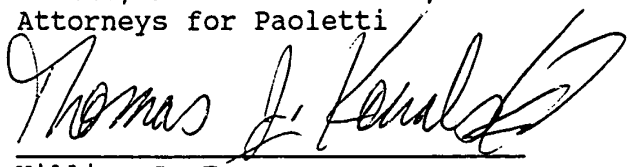
variation of the teachings of any or all of the '330 Patent, the Panicali et al. PNAS article, the Panicali et al. Abstract, the Panicali et al. ASV presentation, and the Paoletti laboratory CSH presentation, alone, or in view of any or all of Venkatesan, Weir and Hruby 1982, or, optionally in further view of any or all of the documents concerning other vectors discussed above.

CONCLUSION

The claims of Moss should be held unpatentable under 35 U.S.C. §102/103 over the prior art, judgment and an award of priority should be granted in favor of Paoletti; and, such is respectfully requested.

Respectfully submitted,

CURTIS, MORRIS & SAFFORD, P.C.
Attorneys for Paoletti



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454310-5010

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true copy of the foregoing PAOLETTI ET AL. MOTION UNDER 37 C.F.R. §§ 1.633 AND 1.637 FOR JUDGMENT ON GROUND THAT MOSS ET AL. CLAIMS NOT PATENTABLE TO MOSS ET AL. is being served upon the party MOSS ET AL. on this 13th day of March, 1995 by posting said true copy by first class mail, postage prepaid to the lead attorney for MOSS ET AL. at his address of record, namely:

Stephan A. Bent
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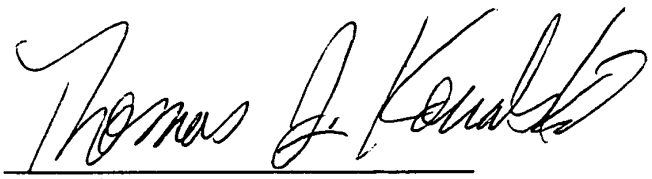
By: 

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PATENT
454310-5010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

PAOLETTI, ET AL.	)	
	)	
V.	)	Interference 103,399
	)	
MOSS, ET AL.	)	Administrative Patent Judge Andrew H. Metz
	)	

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231, BOX INTERFERENCE
on March 13, 1995

THOMAS J. KOWALSKI, REG. NO. 32,147
Name of Applicant, Assignee or Registered Representative

Thomas J. Kowalski
Signature

13 Mar 95
Date of Signature

PAOLETTI ET AL. MOTION UNDER 37 C.F.R. §1.633(a) AND (g) FOR JUDGMENT ON GROUND THAT MOSS ET AL. CLAIMS NOT PATENTABLE TO MOSS ET AL. FOR FAILING TO POINT OUT AND DISTINCTLY CLAIM THE SUBJECT MATTER OF THE INVENTION

The Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX INTERFERENCE

Sir:

PAOLETTI ET AL. ("Paoletti") hereby moves before the Board of Patent Appeals and Interferences under 37 C.F.R. §1.633(a) and (g) and any other Rules of the Commissioner for judgment on the ground that the party Moss et al. claims

corresponding to the Count in Moss's application Serial No. 07/987,546, filed December 7, 1992 (hereinafter "the Moss application") are unpatentable for failure to comply with the requirements of 35 U.S.C. §112, second paragraph.

Specifically, the claims of the Moss application do not particularly point out and distinctly claim the subject matter which is regarded by Moss as the invention, as required by 35 U.S.C. §112, second paragraph. Nor do applications from which the Moss application claims priority, i.e. Serial No. 07/539,169, filed June 18, 1990; Serial No. 07/072,455, filed July 13, 1987; Serial No. 06/555,811, filed November 28, 1983; Serial No. 06/445,892, filed December 1, 1982; and Serial No. 06/445,451, filed November 30, 1982, contain claims or disclosure which point out and distinctly claim the subject matter which is regarded by Moss as the invention. Therefore, Moss' claims corresponding to the Count are unpatentable, and should not be accorded the benefit of these applications' filing dates. Since patentability is a threshold determination in an Interference, and Moss' claims corresponding to the Count are unpatentable, Paoletti should be awarded judgment.[1]

---

[1] A concurrently filed Motion attacks the benefit accorded Moss in the declaration of Interference and, to the extent necessary, is incorporated herein by reference.

FACTS

(1) Moss claims 33, 36, 37, 39, 41-44, 47, 48, 50 and 52-57 of Moss application Serial No. 07/987,546, filed December 7, 1992, were designated as corresponding to the Count.

(2) The independent claims of the Moss application corresponding substantially to the single Count of the interference are claim 33, directed to a plasmid, claim 44, directed to a recombinant vaccinia virus, claim 55, directed to a method for preparing a vector, and claim 57, directed to a method for producing a protein, all of which comprise a vaccinia virus promoter sequence and a foreign DNA sequence, wherein the promoter "is adjacent to and exerts transcriptional control over" the foreign gene.

(3) The present Count is Moss et al. claim 44, which reads:

> A recombinant vaccinia virus that comprises a segment comprised of (A) a first DNA sequence encoding a polypeptide that is foreign to vaccinia virus and (B) a vaccinia promoter sequence, wherein (i) said promoter sequence is adjacent to and exerts transcriptional control over said first DNA sequence and (ii) said segment is positioned within a nonessential genomic region of said recombinant vaccinia virus.

(4) In the preliminary amendment to Moss application Serial No. 07/539,169 (of which Moss application Serial No. 07/987,546 is a file wrapper continuation), Moss amended the claims to include the "adjacent to" limitation and attempted to

distinguish the Moss application from the invention of Paoletti et al. by stating:

> [N]one of the documents in question [i.e., papers reporting the work of Drs. Panicali and Paoletti] disclosed a poxvirus construct wherein, as presently recited, a foreign structural sequence was under the control of a poxvirus transcriptional regulatory sequence that was also adjacent to the structural sequence [emphasis added].

In discussing the importance of the "adjacency" limitation, Moss further asserts the "adverse impact of an open reading frame separating a viral promotor from a structural sequence."

(5) The application was amended June 18, 1990 to include dependent claims 34, 35, 45, 46, 58, 59 and 60, which differed from the independent claims from which they depended in that they contained either the limitation that "said promoter sequence is not separated from said first DNA sequence by another promoter sequence" or the limitation that "said promoter sequence is not separated from said first DNA sequence by a DNA sequence coding for a vaccinia protein or portion thereof."

(6) In the Office Action dated June 24, 1993, Examiner Mosher rejected claims 34, 35, 45, 58 59, and 60 under 35 U.S.C. §112, fourth paragraph as being of improper dependent form for failing to further limit the subject matter of a previous claim. In support of this rejection, the Examiner stated:

> Independent claims 33, 44, 55 and 57 require a vaccinia virus promoter adjacent to a first

DNA sequence encoding a polypeptide that is foreign to vaccinia virus. This element of "adjacent"-ness was seen as the element which distinguished the claimed invention from Paoletti PN 4,769,330, leading to the withdrawal of the rejection that had been made under 35 U.S.C. §102(e)/103 in paper 6. Paoletti was seen as lacking the "adjacent" element of the claims, since the constructs of Paoletti contained at least an HSV TK coding sequence, between the endogenous vaccinia promoter and the foreign coding sequence. The instant specification does not explicitly define "adjacent". Webster's dictionary has been consulted for the ordinary meaning of the term: "Adjacent may or may not imply contact but always implies absence of anything of the same kind in between." If the term adjacent implies the absence of anything of the same kind in between, then claims 34, 35, 45, 46, 58, 59 and 60 fail to further limit, as the sequences cannot be adjacent and also be separated by another promoter sequence or by sequence coding for vaccinia protein or portion thereof. Alternatively, if applicants intend "adjacent" to encompass separation of the promoter and the foreign sequence by another promoter sequence, or by vaccinia protein coding sequence, then the withdrawal of the 102/103 rejection may require reconsideration [emphasis added].

(7) In the Amendment filed October 22, 1993, Moss canceled claims 34, 35, 45, 46, 58, 59 and 60, implying that "adjacent to" was intended to mean the absence of another promoter sequence, sequence coding for vaccinia protein, or portion thereof, without, however, directly addressing the issue and providing a definition of the term "adjacent to," or explicitly incorporating the limitations of the canceled claims into the remaining independent claims.

(8) In the specification at page 13, and the January 27, 1994 Preliminary Amendment to application Serial No. 07/987,546, Moss cites Venkatesan et al., Cell 125:805-813 (September 1981) (copy attached as Exhibit 1) for its teachings regarding the mapping of vaccinia start codons. The title of this publication is "Distinctive Nucleotide Sequences *Adjacent to* Multiple Initiation and Termination Sites of an Early Vaccinia Virus Gene" [emphasis added]. This article reports the discovery of a promoter DNA sequence "immediately upstream" of the initiation of translation site for a gene encoding a 7.5 Kd polypeptide. There are no intervening nucleotides between the promoter sequence and the mRNA translation start site disclosed in this reference. This is what "adjacent to" must mean in the art; not a dictionary definition to laymen, as relied upon by the Examiner.

ARGUMENT

The second paragraph of Section 112 requires that a patent application contain "one or more claims particularly pointing out and distinctly claiming what the applicant regards as his invention." 35 U.S.C. §112. The standard for determining whether this requirement of definiteness in the claims is satisfied is "whether one skilled in the art would understand the bounds of the claim when read in light of the specification." Miles Laboratories, Inc. v. Shandon, Inc., 27 U.S.P.Q.2d 1123, 1127 (Fed. Cir. 1993), cert. denied, 114 S.Ct. 943 (1994). The degree of precision required will vary depending on the nature of the subject matter claimed. Id.

I. CLAIMS 33, 36, 37, 39, 41-44, 47, 48, 50 AND 52-57 OF THE MOSS PATENT ARE UNPATENTABLE BECAUSE THE TERMS "ADJACENT TO" AND "PROMOTER" CONTAINED THEREIN ARE INDEFINITE

All of the claims corresponding to the Count refer to the phrase "wherein said promoter sequence is adjacent to ... said first DNA sequence." The term "adjacent" to is not defined in the claims or any Moss application, and it is not clear what Moss intends "adjacent to" to mean. "Adjacent to" could mean that nucleotide sequences which do not function as regulatory sequences in the system are permitted. On the other hand, the term "adjacent to" could be intended to exclude any intervening nucleotides.

Reference to the specification, or to the specifications of the applications from which Moss claims priority, does not clarify this issue. In fact, throughout the prosecution of this family of applications, Moss has used numerous terms, whose meanings seem to vary with each appearance, to describe the relationship of the promoter sequence to the foreign DNA sequence, without ever adequately defining any of them. This fluctuation of terminology can be seen in the following table [emphasis added]:

06/445,451	
Abstract	chimeric gene = "vaccinia virus transcriptional regulatory sequences [combined] with uninterrupted foreign protein coding sequences *in vitro*"
p. 5 ll. 20-21	"a foreign gene ... is ligated next to the vaccinia promoter"
p. 10 ll. 6-9	"The protein coding segment of the foreign gene was ligated directly to the promoter when it had complementary termini or after modification of its ends"
p. 10 ll. 13-14	"The desired plasmid had the promoter adjacent to the start of the foreign gene"
p. 20 ll. 20-22	Both of these vectors [containing vaccine promoter sequence] have BamHI and SmaI restriction sites for insertion of foreign genes downstream "from the translocated vaccine 7.5K gene promoter."
p. 24 ll. 1-4	"The resulting plasmid designated pMM3 contains unique HincII, AccI, SalI, BamHI and SmaI sites for insertion of foreign genes next to the thymidine kinase promoter"
06/445,892	
Abstract	"... infectious vaccinia virus recombinants that contain the hepatitis B virus surface antigen (HBsAg) gene linked to a vaccinia virus promoter..."
p. 4 ll. 3-4	"Chimeric genes, consisting of a vaccinia virus transcriptional regulatory sequence ligated to an HBsAg coding sequence ...."
p. 4 l. 31 - p. 5 ll. 1-2	"Each of the plasmids were designed so that restriction endonuclease sites would be available for any foreign protein coding sequence to be inserted next to a vaccinia virus promoter"

06/555,811	
p. 5 ll. 16-20	"The chimeric gene has the transcriptional regulatory signals and RNA start site of a vaccinia virus gene adjacent to the translational start site and foreign protein coding sequence of a foreign gene."
pp. 20-21 claim 4	"The composition of claim 1 wherein the recombinant virus is a vaccinia virus recombinant containing a chimeric gene consisting of defined vaccinia virus transcriptional regulatory sequences joined to hepatitis B virus surface antigen coding sequences."
07/072,455	
p. 1 ll. 4-6	"This invention provides recombinant vaccinia virus synthetically modified by insertion of a chimeric gene containing vaccinia regulatory sequences or DNA sequences functionally equivalent thereto flanking DNA sequences which in nature are not contiguous with the flanking vaccinia regulatory DNA sequences."
p. 1 ll. 25-27 to p. 2 ll. 1-5	"In a preferred embodiment of the invention expression of foreign DNA is obtained by forming a chimeric gene consisting of a vaccinia virus transcriptional regulatory sequence and an uninterrupted protein coding sequence of a foreign gene. The vaccinia virus transcriptional regulatory sequence consists of a DNA sequence that precedes and may include the site at which RNA synthesis begins."
p. 2 ll. 16-17	"... a foreign gene with complementary termini is ligated next to the vaccinia virus promoter."
p. 8 ll. 5-14	"The protein coding segment of the foreign gene was ligated directly to the promoter when it had complementary termini or after modification of its ends .... The desired plasmid had the promoter adjacent to the start of the foreign gene."
p. 54 claim 29	"A vector comprising: (1) a plasmid; (2) a chimeric gene having at least one poxvirus transcriptional regulatory sequence and at least one uninterrupted protein coding sequence from a foreign gene; and (3) DNA from a non-essential region of the poxvirus genome flanking the chimeric gene."

7/24/89 Amendment	"... the present invention is directed to a purposefully constructed cassette comprising a vaccinia promoter linked to a foreign DNA."
Preliminary Amendment, claim 33	"A plasmid that comprises (A) a segment comprised of (i) a first DNA sequence encoding a polypeptide that is foreign to poxvirus and (ii) a poxvirus transcriptional regulatory sequence is adjacent to and exerts transcriptional control over said first DNA sequence ...."
07/539,169	
Preliminary Amendment, claim 33	"A plasmid that comprises (A) a segment comprised of (i) a first DNA sequence encoding a polypeptide that is foreign to poxvirus and (ii) a poxvirus transcriptional regulatory sequence is adjacent to and exerts transcriptional control over said first DNA sequence..."
Preliminary Amendment, pp. 12-13, bridging ¶	"... [A] construct within the present invention includes a poxvirus TRS purposefully placed in a predetermined relation to a polypeptide-encoding sequence.

Nowhere are these varying terms clarified, and looking at them in the context in which they appear only confuses matters further. See, e.g., the specification at page 8, lines 10-14 of the Moss application, describing the construction of a plasmid containing a vaccinia promoter and a foreign gene:

> When the foreign gene was unsuitable in more than one orientation, it was necessary to analyze by restriction endonuclease digestion and gel electrophoresis or nucleotide sequencing to check that the proper one was obtained. The desired ... had the promoter adjacent to the start of the foreign gene.

In this context, "adjacent to" seems to mean that the start of the foreign gene is proximal to the promoter as opposed to

distal; in other words, it refers to the orientation of the foreign gene vis-a-vis the promoter, not the presence or absence of intervening sequences.

Moreover, the concept of "adjacent to" is a relative concept whose interpretation is further confused when one looks to the prosecution history of this line of cases. Moss claims 34, 44, 59 and 60, now canceled, called for the promoter and the first DNA sequence not to be separated by another promoter sequence (presumably another vaccinia virus promoter sequence, although as discussed above, this is far from clear). Moss' claim 58, now canceled, called for the vaccinia virus promoter sequence and the first DNA sequence not to be separated "by another transcriptional regulatory sequence." Moss' now-canceled claims 35 and 46 called for the vaccinia virus promoter sequence and the first DNA sequence not to be separated by a DNA sequence coding for a vaccinia protein or portion thereof. Although the Examiner required cancellation of these claims asserting that these concepts were included by the term "adjacent to," the limitations of these dependent claims were not required to be inserted into Moss' independent claims. Thus, it is not clear whether Moss' claims are limited by these unstated recitations, although it appears that the Examiner intended that these claims be so limited in deciding to allow the independent claims.

Nonetheless, these now-canceled dependent claims help to highlight the indefiniteness and lack of clarity of "adjacent

to", especially in light of the doctrine of claim differentiation.

The doctrine of claim differentiation requires that each claim must be different from every other claim, so that claims should be interpreted to differentiate each from the others wherever possible. Laitram Corp. v. Cambridge Wire Cloth Co., 9 U.S.P.Q.2d 1289 (Fed. Cir. 1988). Thus, where a claim omits an element included in other claims, such an omission is presumed to be intentional. Tandon Corp. v. I.T.C., 4 U.S.P.Q.2d 1283 (Fed. Cir. 1987). Where there are both broad and narrow claims, the narrow claim limitations cannot be read into the broad claims, either to avoid invalidity or to escape infringement. Kalmar v. Kimberly-Clark Corp., 218 U.S.P.Q. 781, 788 (Fed. Cir. 1983), cert. denied 224 U.S.P.Q. 520 (1984).

Moss claim 36 calls for the claim 33 plasmid to consist essentially of segment (A) (comprising a foreign DNA sequence encoding a polypeptide and a vaccinia virus promoter sequence) and DNA (B) from a nonessential region of a vaccinia genome, and provides that the first DNA sequence comprises an translational initiation codon. Likewise, Moss claim 47 calls for the claim 44 recombinant to consist essentially of (A) and (B), and for the first DNA sequence to comprise a translational initiation codon. Thus, because under the doctrine of claim differentiation the limitations of the narrower dependent claims 36 and 47 cannot be read into the broader claims 33 and 44, the plasmid of Moss claim

33 and the recombinant of Moss claim 44 can include DNA in addition to (A) and (B) and the flanking DNA; in other words, non-coding vaccinia or foreign DNA between (A) and (B) are not excluded from Moss claims 33 and 44 (and, if such is intended to be excluded, that intention is not clear from the indefinite, undefined term "adjacent to").

Further, claims 37 and 48 call for the promoter to be from DNA not contained within the nonessential region. This concept of the nature of the promoter also reinforces the conclusion that Moss' "adjacent to" and "promoter" concepts are unclear and indefinite. Indeed, claims 37 and 48 seem to exclude recombinants in which the "segment" is in the vaccinia virus HindIII fragment (thymidine kinase or "TK" region) and the "promoter" is the vaccinia virus TK promoter.

While an ordinary dictionary, as used by the Examiner in her attempt to resolve this issue, is usually very useful for determining the definition of an unclear term, when the term is used in a technical context, as is the case here, there are more appropriate ways to determine its meaning. One way is to ascertain how the term has been used by others skilled in the art. In Venkatesan, Exhibit 1, "adjacent to" is used to describe the relationship between an AT-rich DNA sequence believed to be the promoter for a gene coding for a 7.5kd polypeptide, and the transcription initiation site of that gene. The promoter sequence is also described as "immediately upstream" of the

initiation of transcription site of that gene (page 805). The DNA sequence around the 5'-end of the mRNA transcription initiation site shown in Figure 3 of the reference indicates that there are no intervening nucleotides between the promoter sequence of the transcription initiation site. The declaration of Dr. Dennis Hruby is attached as Exhibit 2 to provide an expert's explanation of the Venkatesan article.

It would be expected that "adjacent to" would have the same meaning when used in a similar context in the Moss application, (note Moss arguments in the January 27, 1993 Preliminary Amendment in USSN 07/987,456, at 12-15, especially at page 13 wherein Moss cites Venkatesan for Section 112 enablement purposes). However, in view of the effect of the doctrine of claim differentiation on the interpretation of these claims and the fact that the chimeric genes exemplified by the Moss specification all include intervening DNA between the promoter sequence and the gene it is supposed to be "adjacent to"[2], this conclusion is far from certain.

As a result of Moss' use of the indefinite term "adjacent to" and failure to define it, one skilled in the art would be unable to determine the scope of the claims. In other

---

[2] See "Paoletti Motion Under 37 C.F.R. §1.133(a) and (g) for Judgement on Ground That Moss et al. Claims Not Patentable to Moss et al. For Failure to Provide an Enabling Disclosure and an Adequate Written Description," filed concurrently herewith, for a discussion of this issue.

words, the skilled artisan would be unable to determine whether the Moss claims read on recombinant vaccinia virus containing a vaccinia promoter element which exerted transcriptional control over a foreign gene sequence but was separated from that foreign DNA sequence by extraneous DNA. Since the patentability of Moss claims over the prior art was predicated specifically on the limitation that the promoter be "adjacent to" the foreign DNA sequence, this limitation is necessarily material.

The Federal Circuit has held that "[w]hen the meaning of claims is in doubt, especially when ... there is close prior art, they are properly declared invalid." Amgen Inc. v. Chugai Pharmaceutical Co., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). The terms used in the Moss claims are so vague and indefinite as to create doubts about the claims' scope, in contradiction to the mandate of Section 112. In view of the materiality of the limitation in question, the precision required by the nature of the subject matter of the claims, and the closeness of the prior art, the vagueness and indefiniteness of the claim language renders the Moss claims unpatentable.

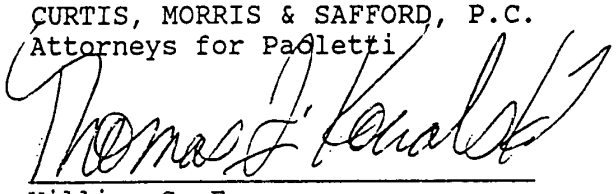
CONCLUSION

In view of the foregoing, it is clear that claims 33, 36, 37, 39, 41-44, 47, 48, 50 and 52-57 of the Moss application and the applications from which it claims priority fail to point out and distinctly claim the subject matter which Moss regards as the invention in accordance with 35 U.S.C. §112, second

paragraph. Accordingly, claims 33, 36, 37, 39, 41-44, 47, 48, 50 and 52-57 corresponding to the Count are unpatentable to Moss, and Moss should not be accorded the benefit of the prior applications. Therefore, Paoletti should be awarded priority of invention, and such award is respectfully requested.[3]

Respectfully submitted,

CURTIS, MORRIS & SAFFORD, P.C.
Attorneys for Paoletti



William S. Frommer
Reg. No. 25,506
Robert F. Kirchner
Reg. No. 31,034
Thomas J. Kowalski
Reg. No. 32,147
Pamela G. Salkeld
Reg. No. 38,607

---

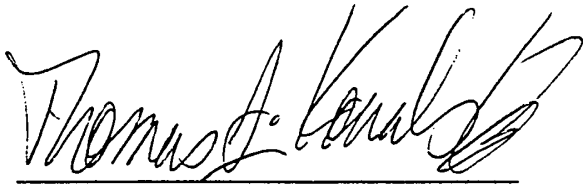
[3] To any extent necessary, this Motion is also to be construed as a Motion for an immediate testimony period on the issues of enablement, written description, clarity, definiteness, entitlement to benefit of earlier applications and patentability of Moss claims, and the art with respect thereto because immediate determination of these issues can determine which party is senior or junior (i.e., the burden of proof), and whether an interference is necessary at all (because if Moss is not entitled to a filing date or otherwise unable to overcome the prior art, there is no need for an Interference).

PATENT
454310-5010

CERTIFICATE OR SERVICE

The undersigned hereby certifies that a true copy of the foregoing PAOLETTI ET AL. MOTION UNDER 37 C.F.R. §1.633(a) AND (g) FOR JUDGMENT ON GROUND THAT MOSS ET AL. CLAIMS NOT PATENTABLE TO MOSS ET AL. FOR FAILING TO POINT OUT AND DISTINCTLY CLAIM THE SUBJECT MATTER OF THE INVENTION is being served upon the party MOSS ET AL. on this 13th day of March, 1995 by posting said true copy by first class mail, postage prepaid to the lead attorney for MOSS ET AL. at his address of record, namely:

Stephan A. Bent
FOLEY & LARDNER
3000 K. Street, N.W.
Suite 500
Washington, D.C. 20007-5109



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PATENT
454310-5010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

PAOLETTI, ET AL.	)	
	)	
V.	)	Interference 103,399
	)	
MOSS, ET AL.	)	Administrative Patent Judge Andrew H. Metz
	)	
	)	

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231, BOX INTERFERENCE
on March 13, 1995

THOMAS J. KOWALSKI, REG. NO. 32,147
Name of Applicant, Assignee or Registered Representative

Signature

13 Mar 95
Date of Signature

PAOLETTI ET AL. MOTION UNDER 37 C.F.R. §1.633(a) AND (g) FOR JUDGMENT ON GROUND THAT MOSS ET AL. CLAIMS ARE NOT PATENTABLE TO MOSS ET AL. FOR FAILING TO PROVIDE AN ENABLING DISCLOSURE AND AN ADEQUATE WRITTEN DESCRIPTION

The Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX INTERFERENCE

Sir:

PAOLETTI ET AL. ("Paoletti") hereby moves before the Board of Patent Appeals and Interferences under 37 C.F.R. §1.633(a) and (g) and any other Rules of the Commissioner for judgment on the ground that the party Moss et al. ("Moss") claims

corresponding to the Count are unpatentable for failure to comply with the requirements of 35 U.S.C. §112, first paragraph.

Specifically, Moss's application Serial No. 07/987,546, filed December 7, 1992 (hereinafter "the Moss application"), does not contain an adequate written description of the claimed subject matter, nor does it enable one to practice the invention thereof, as required by 35 U.S.C. §112, first paragraph. The applications from which the Moss application claims priority, i.e., Serial No. 07/539,169, filed June 18, 1990; Serial No. 07/072,455, filed July 13, 1987; Serial No. 06/555,811, filed November 28, 1983; Serial No. 06/445,892, filed December 1, 1982; and Serial No. 06/445,451, filed November 30, 1982 also lack an adequate written description and enabling description of the claimed subject matter. Therefore, Moss' claims corresponding to the Count are unpatentable, and should not be accorded the benefit of these applications' filing dates. Since patentability is a threshold determination, and Moss' claims corresponding to the Count are unpatentable, Paoletti should be awarded judgment. A concurrently filed Motion attacks the benefit accorded Moss in the declaration of Interference and, to the extent necessary, that Motion is incorporated herein by reference.

FACTS

(1) Moss claims 33, 36, 37, 39, 41-44, 47, 48, 50 and 52-57 of Moss application Serial No. 07/987,546, filed December 7, 1992, were designated as corresponding to the Count.

(2) The independent claims of the Moss application corresponding substantially to the single Count of the interference are claim 33, directed to a plasmid, claim 44, directed to a recombinant vaccinia virus, claim 55, directed to a method for preparing a vector, and claim 57, directed to a method for producing a protein, all of which comprise a vaccinia virus promoter sequence and a foreign DNA sequence flanked by DNA from a nonessential region of a vaccinia genome, wherein the promoter "is adjacent to and exerts transcriptional control over" the foreign gene.

(3) Claim 57 reads as follows:

> A method for producing a protein, comprising the steps of
>
> (A) providing a recombinant vaccinia virus that contains a segment comprised of (i) a first DNA sequence encoding a polypeptide that is foreign to vaccinia virus and (ii) a vaccinia virus promoter, wherein (a) said promoter sequence is adjacent to and exerts transcriptional control over said first DNA sequence and (b) said segment is positioned within a nonessential genomic region of said recombinant vaccinia virus;
>
> (B) infecting host cells with said recombinant vaccinia virus such that

said host cells express said polypeptide; and then

(C) separating said polypeptide from said host cells.

(4) The present Count is Moss et al. claim 44 which reads:

> A recombinant vaccinia virus that comprises a segment comprised of (A) a first DNA sequence encoding a polypeptide that is foreign to vaccinia virus and (B) a vaccinia virus promoter sequence, wherein (i) said promoter sequence is adjacent to and exerts transcriptional control over said first DNA sequence and (ii) said segment is positioned within a nonessential genomic region of said recombinant vaccinia virus.

(5) The Moss specification specifically discloses the preparation of chimeric genes containing vaccinia promoter sequences and six different DNA sequences which encode polypeptides foreign to vaccinia virus. All of these chimeric genes have been shown, as discussed infra, to contain extraneous DNA sequences between the vaccinia promoter sequence and the foreign DNA sequence.

(6) The application was amended June 18, 1990 to include dependent claims 34, 35, 45, 46, 58, 59 and 60, which differed from the independent claims from which they depended in that they contained either the limitation that "said promoter sequence is not separated from said first DNA sequence by another promoter sequence" or the limitation that "said promoter sequence

is not separated from said first DNA sequence by a DNA sequence coding for a vaccinia protein or portion thereof."

(7) In the Office Action dated June 24, 1993, Examiner Mosher rejected claims 34, 35, 45, 46, 58, 59 and 60 under 35 U.S.C. §112, fourth paragraph as being of improper dependent form for failing to further limit the subject matter of a previous claim. In support of this rejection, the Examiner stated:

> Independent claims 33, 44, 55, and 57 require a vaccinia virus promoter adjacent to a first DNA sequence encoding a polypeptide that is foreign to vaccinia virus. This element of "adjacent"-ness was seen as the element which distinguished the claimed invention from Paoletti PN 4,769,330, leading to the withdrawal of the rejection that had been made under 35 USC §102(e)/103 in paper 6. Paoletti was seen as lacking the "adjacent" element of the claims, since the constructs of Paoletti contained at least an HSV TK promoter, and probably also some vaccinia coding sequence, between the endogenous vaccinia promoter and the foreign coding sequence. The instant specification does not explicitly define "adjacent". Webster's dictionary has been consulted for the ordinary meaning of the term: "Adjacent may or may not imply contact but always implies absence of anything of the same kind in between." If the term adjacent implies the absence of anything of the same kind in between, then claims 34, 35, 45, 46, 58, 59, 60 fail to further limit, as the sequences cannot be adjacent and also be separated by another promoter sequence or by sequence coding for vaccinia protein or portion thereof. Alternatively, if applicants intend "adjacent" to encompass separation of the promoter and the foreign sequence by another promoter sequence, or by vaccinia protein coding sequence, then the withdrawal of the 102/103 rejection may require reconsideration [emphasis added].

(8) In the Amendment filed October 22, 1993, Moss canceled claims 34, 35, 45, 46, 58, 59 and 60, implying that "adjacent to" was intended to mean the absence of another promoter sequence, sequence coding for vaccinia protein, or portion thereof, without, however, directly addressing the issue and providing a definition of the term "adjacent to."

ARGUMENT

I. THE MOSS CLAIMS ARE NOT ENABLED

The first paragraph of Section 112 requires that the specification contain a description of the claimed invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." One skilled in the art must be able to practice the claimed invention without undue experimentation. In re Wright, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993); White Consolidated Indus., Inc. v. Vega Servo-Control, Inc., 218 U.S.P.Q. 961 (Fed. Cir. 1983). The specification must be enabling for the invention as broadly as it is claimed. In re Goodman, 29 U.S.P.Q. 2010, 2013.

When an applicant wishes to claim the benefit of an earlier application, the applicant bears the burden of proving that the earlier application complies with the enablement requirement of Section 112. Fiers v. Sugano, at 1605-06.

A. The claim language "wherein said promoter sequence is adjacent to...said first DNA sequence" is not enabled by Any Moss specification

All claims corresponding to the Count refer to a chimeric gene wherein a vaccinia virus promoter is "adjacent to" a DNA sequence encoding a polypeptide that is foreign to vaccinia virus. The meaning of the term "adjacent to" is not clear. It not defined or any Moss application. If it is intended to mean that nucleotide sequences which do not function as regulatory sequences in the system are permitted, then the claims appear to lack novelty and/or unobviousness over the prior art, as discussed by Examiner Mosher in the Office Action dated June 24, 1993 (See also Paoletti's Motion asserting unpatentability of Moss' claims under 35 U.S.C. §102/103, incorporated herein by reference). Furthermore, it would require undue experimentation to determine what intervening sequences could be present between the promoter and the foreign DNA and still produce a functional gene (Since Moss gives no guidance as to any degree of "adjacency").

If, on the other hand, the term "adjacent to" is intended to exclude any intervening nucleotides, the claims corresponding to the Count are not enabled to allow one skilled in the art to carry out the subject matter of the claims, because the disclosure of the specification is limited to examples wherein there are extraneous DNA sequences between the vaccinia

promoter element and the translation initiation site of the foreign gene, and there is no teaching in any Moss application that a recombinant vaccinia virus without such extraneous DNA would be operable.

Construction and sequencing of the chimeric genes disclosed by Moss has shown that there are extraneous DNA sequences between the vaccinia promoter and the translation initiation site of the foreign gene. The disclosure of extraneous DNA sequences between the promoter element and translation initiation codon of the foreign gene in the Moss application Serial No. 07/987,546 is as follows:

Example 1: 7.5K promoter element. The 275bp 7.5K promoter element contains the vaccinia 7.5K promoter including the transcriptional start site and 30 bp of vaccinia DNA downstream from the transcriptional start site. The element does not include the vaccinia 7.5K translational initiation codon (ATG) or 18 bp of vaccinia DNA immediately preceding the ATG (Venkatesan et al. Cell 125:805-813 (1981); copy attached as Exhibit 1). The 7.5K promoter element was cloned into pUC9 (Messing, in Methods in Enzymology 101:20-78 (1983); copy attached as Exhibit 2) cut with HincII, resulting in plasmid pGS15 and its derivative, pGS19. A promoter element from pGS19 was inserted in both orientations into the EcoRI site within coding sequences of the vaccinia thymidine kinase gene, resulting

in plasmids pGS20 and pGS21. These plasmid vectors were used for the construction of chimeric genes. In all cases, such chimeric genes contain at least 3 bp of extraneous DNA derived from the pUC9 multicloning region and located between the vaccinia transcriptional regulatory element and DNA encoding the foreign gene.

Example 2: Vaccinia TK promoter; plasmids pMM1-4. The vaccinia TK locus was modified for use as an insertion site for the introduction of foreign DNA into the vaccinia genome. The left flanking arm includes the vaccinia TK promoter element for the expression in situ of foreign genes. This promoter element includes the vaccinia TK transcriptional initiation site. The element does not include the vaccinia TK translational initiation codon (ATG) or 3 bp of vaccinia DNA immediately preceding the ATG (Weir and Moss, J. Virol. 46:530-537 (1983); copy attached as Exhibit 3). Chimeric genes constructed in plasmid vector pMM4 contain variable amounts of extraneous DNA derived from the pUC9 multicloning region. This DNA is located between the vaccinia TK transcriptional regulatory element and the DNA encoding the foreign gene.

Example 3: CAT gene. The gene encoding chloramphenicol acetyl transferase (CAT) was identified in E. coli transposons. It is used in E. coli plasmids to confer

chloramphenicol resistance (Cm^r). Plasmid pBR328 (Soberon et al., Gene 9:287-305 (1980); copy attached as Exhibit 4) is a derivative of pBR325. The sequence of the CAT gene (Cm^r gene) common to both plasmids is published (Prentki et al., Gene 14:289-299 (1981)).

A 770 bp TaqI DNA fragment containing the CAT gene was isolated from plasmid pBR328. The TaqI fragment containing the CAT gene was cloned into pUC7 (Messing, 1983) generating plasmid pGS29. The CAT gene was isolated from PGS29 as a BamHI fragment, and inserted into the BamHI site of plasmid pGS21. The resulting plasmid, pGS24, contains the CAT gene under the transcriptional control of the vaccinia 7.5K promoter. The chimeric gene was inserted into the TK locus of vaccinia virus, resulting in recombinant vaccinia virus vCAT24. In vCAT24 there are 10 bp of extraneous DNA derived from the pUC9 and pUC7 multicloning regions immediately downstream from the vaccinia 7.5K promoter. Additionally, the vaccinia promoter is separated from the translational start codon of the CAT gene by 30 bp of DNA derived from pBR328. The DNA sequence separating the 7.5K promoter region and the CAT translational start codon is as follows. Restriction sites are underlined.

BamHI TaqI

5′ GACGGATCCGTCGAGATTTTCAGGAGCTAAGGAAGCTAAA 3′

Example 4: HSV-TK gene. The sequence of the gene encoding the Herpes Simplex Virus thymidine kinase (HSV-TK) and surrounding region is published (Wagner et al., Proc. Natl. Acad. Sci. USA 78:1441-1445 (1981); copy attached as Exhibit 5). A 1.8kb HincII/PvuII fragment containing the HSV-TK coding sequence was cloned into the HincII site of pUC7, generating plasmid pVH4. The HSV-TK gene was isolated from pVH4 as an EcoRI fragment, and inserted into the EcoRI site of pMM4. The resulting plasmid, pMM20, contains the HSV-TK gene under the transcriptional control of the vaccinia TK promoter element. The chimeric gene was inserted into the TK locus of vaccinia virus. In the resulting recombinant vaccinia virus there are 27 bp of extraneous DNA derived from the pUC9 and pUC7 multicloning regions immediately downstream from the vaccinia TK promoter. Additionally, the vaccinia TK promoter is separated from the translational start codon of the HSV-TK gene by 74 bp of DNA derived from HSV. The DNA sequence separating the vaccinia TK promoter region and the HSV-TK translational start codon is as follows. Restriction sites are underlined.

BamHISmaIEcoRI BamHI HincII BglII

5′ GACGGATCCCGGGAATTCCCCGGATCCGTCAACAGCGTGCCGCAGATCTTGGT

GGCGTGAAACTCCCGCACCTCTTTGGCAAGCGCCTTGTAGAAGCGCGT 3′

Example 5: VSV N gene. Plasmid pJS223 contains a cDNA copy of the nucleoprotein (N) gene from vesicular stomatitis virus (VSV) (Sprague et al., J. Virol. 45:773-781 (1983); copy attached as Exhibit 6). In pJS223 the VSV N gene is preceded by a XhoI site derived from synthetic linkers. A XhoI fragment containing the VSV N gene was isolated from pJS223 and inserted into the SalI site of pMM3. The resulting plasmid, pMM17, contains the VSV N gene under the transcriptional control of the vaccinia TK promoter element. The chimeric gene was inserted into the TK locus of vaccinia virus. In the resulting recombinant vaccinia virus the vaccinia TK promoter element is separated from the translational start codon of the VSV N gene by 31 bp of DNA derived from pJS223. The DNA sequence separating the vaccinia TK promoter region and the VSV N translational start codon is as follows.

5′ GAGGTCAGGAGAAACTTTAACAGTAATCAAA 3′

Examples 6 and 7: HBsAg gene. The DNA sequence of the gene encoding the HBV surface antigen (HBsAg) for the adw subtype is published (Valenzuela et al., Nature 280:815-818 (1979); copy attached as Exhibit 7). A 1350 bp BamHI fragment (Moriarty et al., Proc. Natl. Acad. Sci. USA 78:2606-2610 (1981); copy attached as Exhibit 8) containing the coding sequence for the

HBsAg gene was inserted into plasmid vectors pGS20, pGS21 and pMM3, all cut with BamHI.

Plasmids pHBs2 and pHBs4 contain the HBsAG coding sequences inserted in the correct orientation relative to the translocated 7.5K vaccinia promoter. These chimeric genes were inserted into the TK locus of vaccinia virus, resulting in vaccinia recombinants vHBs2 and vHBs4, respectively. In vHBs2 and vHBs4 there are 3 bp of extraneous DNA derived from the pUC9 multicloning region located immediately downstream from the vaccinia 7.5K promoter element. Additionally, the vaccinia 7.5K promoter is separated from the translational start codon of the HBsAg gene by 127 bp of HBV DNA. The DNA sequence separating the 7.5K promoter region and the HBsAg translational start codon is as follows. Restriction site is underlined.

BamHI

5′ GACGGATCCCAGAGTCAGGGGTCTGTATCTTCCTGCTGGTGGCTCCAGTTCAGGAAC
AGTAAACCCTGCTCCGAATATTGCCTCTCACATCTCGTCAATCTCCGCGAGGACTGGGGA
CCCTGTGACGAAC 3′

Plasmids pHBs5 contains the HBsAg coding sequences inserted in the correct orientation relative to the vaccinia TK promoter. The chimeric gene was inserted into the TK locus of vaccinia virus. In the resulting recombinant vaccinia virus, vHBs5, there are 3 bp of extraneous DNA derived from the pUC9 multicloning region located immediately downstream from the

vaccinia TK promoter element. Additionally, the vaccinia TK promoter is separated from the translational start codon of the HBsAg gene by 127 bp of DNA derived from HBV. The DNA sequence separating the vaccinia TK promoter region and the HBsAg translational start codon is as follows. Restriction site is underlined.

BamHI

5′ GACGGATCCCAGAGTCAGGGGTCTGTATCTTCCTGCTGGTGGCTCCAGTTCAGGAAC
AGTAAACCCTGCTCCGAATATTGCCTCTCACATCTCGTCAATCTCCGCGAGGACTGGGGA
CCCTGTGACGAAC 3′

Nor is there any enabling description of "chimeric genes" wherein there are no intervening nucleotide sequences between the vaccinia virus and translation initiation site of the foreign gene in any of the Moss predecessor applications. In fact, examples 1-5 of Moss application Serial No. 07/987,546 are identical to those of application Serial No. 06/445,451; and, examples 6 and 7 of Moss application Serial No. 07/987,546 are taken directly from application Serial No. 06/445,892.

Further, claims 37 and 48 call for the promoter to be from DNA not contained within the nonessential region. This concept of the nature of the promoter also reinforces the conclusion that Moss' "adjacent to" and "promoter" concepts are not enabled, by either the specification of the pending

application or its predecessors. Indeed, claims 37 and 48 seem to exclude recombinants in which the "segment" is in the vaccinia virus HindIII fragment (thymidine kinase or "TK" region) and the "promoter" is the vaccinia virus TK promoter.

The term "adjacent to" cannot be enabled by the specification if its definition and that of the "promoter" and "foreign gene" change from one application to the next (and sometimes from one location in a given specification to another).

The concept of "adjacent to" can be analogized to a football field of changing yardage between the goalposts (with one goalpost representing the promoter and the other goalpost representing the foreign gene). The goalposts can be considered "adjacent" because there is no third goalpost between them; but how can one make a recombinant vaccinia virus, or play football, if the distance between goalposts (or the length of the "promoter" and "foreign gene") changes from time to time?

This fluctuation in terminology can be seen in the following table (and, in the table set forth below in the written description discussion:

06/445,451	
Abstract	chimeric gene = "vaccinia virus transcriptional regulatory sequences [combined] with uninterrupted foreign protein coding sequences *in vitro*"
p. 5 ll. 20-21	"a foreign gene ... is ligated next to the vaccinia promoter"
p. 10 ll. 6-9	"The protein coding segment of the foreign gene was ligated directly to the promoter when it had complementary termini or after modification of its ends"
p. 10 ll. 13-14	"The desired plasmid had the promoter adjacent to the start of the foreign gene"
p. 20 ll. 20-22	Both of these vectors [containing vaccine promoter sequence] have BamHI and SmaI restriction sites for insertion of foreign genes downstream "from the translocated vaccine 7.5K gene promoter."
p. 24 ll. 1-4	"The resulting plasmid designated pMM3 contains unique HincII, AccI, SalI, BamHI and SmaI sites for insertion of foreign genes next to the thymidine kinase promoter"
06/445,892	
Abstract	"... infectious vaccinia virus recombinants that contain the hepatitis B virus surface antigen (HBsAg) gene linked to a vaccinia virus promoter..."
p. 4 ll. 3-4	"Chimeric genes, consisting of a vaccinia virus transcriptional regulatory sequence ligated to an HBsAg coding sequence ...."
p. 4 l. 31 - p. 5 ll. 1-2	"Each of the plasmids were designed so that restriction endonuclease sites would be available for any foreign protein coding sequence to be inserted next to a vaccinia virus promoter"

06/555,811	
p. 5 ll. 16-20	"The chimeric gene has the transcriptional regulatory signals and RNA start site of a vaccinia virus gene adjacent to the translational start site and foreign protein coding sequence of a foreign gene."
pp. 20-21 claim 4	"The composition of claim 1 wherein the recombinant virus is a vaccinia virus recombinant containing a chimeric gene consisting of defined vaccinia virus transcriptional regulatory sequences joined to hepatitis B virus surface antigen coding sequences."
07/072,455	
p. 1 ll. 4-6	"This invention provides recombinant vaccinia virus synthetically modified by insertion of a chimeric gene containing vaccinia regulatory sequences or DNA sequences functionally equivalent thereto flanking DNA sequences which in nature are not contiguous with the flanking vaccinia regulatory DNA sequences."
p. 1 ll. 25-27 to p. 2 ll. 1-5	"In a preferred embodiment of the invention expression of foreign DNA is obtained by forming a chimeric gene consisting of a vaccinia virus transcriptional regulatory sequence and an uninterrupted protein coding sequence of a foreign gene. The vaccinia virus transcriptional regulatory sequence consists of a DNA sequence that precedes and may include the site at which RNA synthesis begins."
p. 2 ll. 16-17	"... a foreign gene with complementary termini is ligated next to the vaccinia virus promoter."
p. 8 ll. 5-14	"The protein coding segment of the foreign gene was ligated directly to the promoter when it had complementary termini or after modification of its ends .... The desired plasmid had the promoter adjacent to the start of the foreign gene."

p. 54 claim 29	"A vector comprising: (1) a plasmid; (2) a chimeric gene having at least one poxvirus transcriptional regulatory sequence and at least one uninterrupted protein coding sequence from a foreign gene; and (3) DNA from a non-essential region of the poxvirus genome flanking the chimeric gene."
7/24/89 Amendment	"... the present invention is directed to a purposefully constructed cassette comprising a vaccinia promoter linked to a foreign DNA."
Preliminary Amendment, claim 33	"A plasmid that comprises (A) a segment comprised of (i) a first DNA sequence encoding a polypeptide that is foreign to poxvirus and (ii) a poxvirus transcriptional regulatory sequence is adjacent to and exerts transcriptional control over said first DNA sequence ...."
07/539,169	
Preliminary Amendment, claim 33	"A plasmid that comprises (A) a segment comprised of (i) a first DNA sequence encoding a polypeptide that is foreign to poxvirus and (ii) a poxvirus transcriptional regulatory sequence is adjacent to and exerts transcriptional control over said first DNA sequence..."
Preliminary Amendment, pp. 12-13, bridging ¶	"... [A] construct within the present invention includes a poxvirus TRS purposefully placed in a predetermined relation to a polypeptide-encoding sequence.

It is clear, when all of the Moss applications are viewed together, that no enabling disclosure of the term "adjacent to" has been provided by Moss.

B. The Moss application fails to provide an enabling disclosure for steps (B) and (C) of claim 57

Steps (B) and (C) of claim 57 are directed to infecting host cells with a recombinant vaccinia virus containing the chimeric gene described in claim 44, such that the host cells express the polypeptide encoded by the chimeric gene, and separating the polypeptide from said host cells. The specification does not provide a disclosure which enables the production and isolation of any and all polypeptides, as are encompassed by this claim.

As Examiner Ellis recently stated in an Office Action issued in one of Paoletti's copending applications[1],

> it is well known in [the] art that many factors affect the production of a heterologous protein in a eucaryotic cell. These include, *inter alia,* protein cytotoxicity, differences in post-translational modifications, changes in the three dimensional conformation, mRNA stability, the type of promoter, etc.

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[1] Office Action mailed February 15, 1995 in Paoletti et al. application Serial No. 08/228,926, a copy of which is attached as Exhibit 9. Paoletti is moving in concurrently filed Motions to add this application to the Interference, to have claims 33 to 51 of that application designated as corresponding to the Count in the Interference, to be accorded the benefit of USSN 334,456 for Claims 33-51, and, to have claim 42 of that application be substituted for the present Count. To any extent necessary, those Motions are incorporated herein by reference. In particular, as shown in those Motions, the Paoletti disclosure is at least as detailed as Moss' disclosure (if not more, particularly considering the expression reported in Paoletti's U.S. Patents Nos. 4,769,330, 4,603,112 and 4,722,848).

If Examiner Ellis' view of the unpredictability of this area is correct (and such is not necessarily admitted herein), then the mere expression of five genes in cultures of eukaryotic cells is insufficient evidence to claim that any and all polypeptides can be expressed in eukaryotic cells transfected with a recombinant vaccinia virus containing the gene encoding that polypeptide.

Under Examiner Ellis' view (without necessarily admitting anything as to the correctness of her position), the Moss specification also fails to provide a disclosure sufficient to enable the isolation of any and all polypeptides that might be produced by cells transfected with recombinant vaccinia viruses containing DNA encoding heterologous proteins. As Examiner Ellis further noted in that Office Action,

> [a] recent publication, Bio Critical Synergy: The Biotechnology Industry and Intellectual Property Protection, Presentations of the Intellectual Property Committee of the Biotechnology Industry Organization at the October 17, 1994 Hearing of the U.S. Patent and Trademark Office, San Diego, CA teaches that as recently as 1994, "purification of any protein involves many steps which often must be practiced in a precise order and under specific conditions of time, temperature, volume concentration, etc. These steps are not self-evident, and vary radically from protein to protein. There are a literally infinite [number of] combinations of columns, gradients, gels, precipitants, centrifugations, all with buffers of varying pH, salt, buffers, concentrations of same, etc., to choose from. Until it has been done, and the protein described, there is little guidance as to which way to go." See

> p. 104. The publication further teaches that "[t]he requirements of purifications vary so much from protein to protein, that the knowledge gained from purifying one protein can be useless in devising a protocol to purify another and in fact a detergent or other element used successfully in one protocol can inactivate or destroy another protein. An assay of a protein doesn't tell the person skilled in the art where to begin, or what steps to take." See p. 105.

Accordingly, given the very limited teachings of the Moss application and the unpredictable nature of gene expression and protein isolation (in Examiner Ellis' view), one skilled in the art would be unable to practice the invention of claim 57 without undue experimentation. Simply, if Examiner Ellis is correct, her assertions must also apply against Moss Claim 57.

Thus, in view of the foregoing, the Moss specification does not provide an enabling disclosure which supports claims containing the limitation "wherein said promoter sequence is adjacent to...said first DNA sequence." The Moss application, and its predecessors from which it claims priority, therefore do not comply with the enablement requirement of 35 U.S.C. §112, first paragraph, and accordingly, Moss' claims corresponding to the Count are unpatentable. Paoletti should be awarded priority

and judgment[2].

II. THE MOSS CLAIMS LACK AN ADEQUATE WRITTEN DESCRIPTION

The description requirement of the first paragraph of Section 112 is discussed in Vas-Cath v. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In discussing the distinction between the enablement and written description requirements of Section 112, the Vas-Cath court stated:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed* [emphasis in original.

Id. at 1117; see also In re Smith, 178 U.S.P.Q. 620 (C.C.P.A. 1973). The degree of descriptiveness required to meet this requirement varies depending upon the subject matter of the claimed invention. Fiers v. Sugano, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993).

When an applicant wishes to claim the benefit of an earlier application, the applicant bears the burden of proving

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[2] At page 6 of application Serial No. 07/072,455 Moss asserts that the nucleotide sequence and a precise translational map is need to practice Moss. It is therefore additionally submitted that Moss' claims should be limited to specific promoters. Note too that Moss claims 39 and 50, by not calling explicitly for the vaccinia TK or 7.5 kd polypeptide promoters but rather for that "which regulates" may also be overbroad.

that the earlier application complies with the written description requirement of Section 112. Id. at 1605-06.

Moss now claims a plasmid (in independent claim 33), and a recombinant vaccinia virus (in independent claim 44), both of which comprise a vaccinia virus promoter sequence and a foreign DNA sequence flanked by DNA from a nonessential region of a vaccinia genome, wherein said promoter "is adjacent to and exerts transcriptional control over" the foreign gene. However, this is not described in the specification and thus there is no support for these claims, to the extent that they read on a chimeric gene wherein there are no intervening nucleotides between the vaccinia promoter element and the translation initiation site of the foreign gene. Nor is there any support for these claims in the predecessor applications from which Moss claims priority. The following chart provides a summary of the use of the phrase "adjacent to" with regard to the definition of a chimeric gene in the four Moss specifications:

Moss Application	Presence of phrase "adjacent to"	"chimeric gene" Re "adjacent to"
06/445,451	At page 10, with reference to preparation of plasmid vector to form a chimeric gene.	Page 5, lines 1-14: chimeric gene consisting of vaccinia promoter and foreign gene (protein coding sequence): promoter consists of a DNA segment "preceding and including site at which RNA synthesis begins"; foreign gene includes "site corresponding to initiation of translation." Chimeric gene flanked by vaccinia DNA from a known non-essential region of the genome. P. 29, line 6: pMM20: vaccinia promoter from non-essential region (vvTK promoter with HSV TK flanked by vvTK, but no description generally of "not contiguous" concept), i.e., no written description of promoter from DNA contained or not contained in non-essential region.
06/445,892	Paoletti respectfully invites Moss to locate the phrase; "next to" is used in this application.	N/A
06/555,811	At page 5, with reference to Appln. Serial Nos. 06/445,451 and 06/445,892.	N/A
06/072,455	At page 8, with reference to preparation of plasmid vector to form a chimeric gene.	Page 1, lines 1 to 4: "chimeric gene containing vaccinia regulatory sequences ... flanking DNA sequence which in nature are not contiguous with flanking vaccinia regulatory DNA sequences". Page 1, line 22 to page 2, line 5: promoter is now broadly "sequences that positively regulate ... transcription" and "may" include site at which RNA synthesis begins (contrary to "preceding and including" of USSN 06/445,451); foreign gene "may" include site corresponding to initiation of translation (contrary to "includes" in USSN 06/445,451).

As is shown by this chart, the scope of "adjacency" changed from a longer DNA sequence for the foreign gene in USSN 06/445,451, since "may" in USSN 07/072,455 allows for elimination

of DNA "included" in USSN 06/445,451, and the broadening of "promoter" in USSN 07/072,455 allows for a shorter sequence than that defined as "promoter" in USSN 06/445,451; and from a chimeric gene for which there was no written description of the promoter "not contiguous" with the flanking DNA (i.e., no description of promoter from DNA not contained in non-essential region in USSN 06/445,451) to such a plasmid and recombinant as in dependent Moss claims 37 and 48. See also Moss claims 36 and 47 calling for the foreign gene to comprise a translational initiator codon which is required by the foreign gene definition of USSN 06/445,451, and therefore not by claims 33 and 44, further illustrating how the Moss claims are broader than what is described by earlier Moss applications.

Additionally, the plasmid of claim 36 "consists essentially of" the segment and the non-essential vaccinia DNA, and the recombinant of claim 47 "consists essentially of" the foreign gene and the promoter, thereby raising the issue as to what additional DNA is included by "adjacent to" in claims 33 and 44 and excluded by claims 36 and 47. The transition "consisting essentially of" allows the inclusion of elements that would not materially change the composition within the scope of the claims. To determine which elements are included or excluded by this language, the claims must be read in light of the specification. Ex parte Hoffman, 12 U.S.P.Q.2d 1061 (BOPAI 1989). No guidance

as to what would not materially change the claimed invention is provided by the Moss specification.

Thus, it is not clear that at the date of filing of the Moss application, let alone at the filing dates of the earlier Moss applications, that Moss was in possession of the recombinant vaccinia virus that is the subject matter of this interference. To the extent that it is even possible to determine what the invention is that is being claimed, given the vagueness and indefiniteness of the claim language[3], the specification as originally filed fails to provide an adequate written description of the invention as now claimed. Accordingly, the Moss application and its predecessors from which it claims priority, clearly do not comply with the written description requirement of 35 U.S.C. §112, first paragraph.

CONCLUSION

In view of the foregoing, it is clear that the subject matter of claims 33, 36, 37, 39, 41-44, 47, 48, 50 and 52-57 of the Moss application and the claims of the applications from which it claims priority is not adequately described or enabled in accordance with 35 U.S.C. §112, first paragraph. Accordingly, claims 33, 36, 37, 39, 41-44, 47, 48, 50 and 52-57, corresponding

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[3] See "Paoletti Motion Under 37 C.F.R. §1.633(a) and (g) for Judgment on Ground That Moss et al. Claims Not Patentable to Moss et al. for Failing to Point Out and Distinctly Claim the Subject Matter of the Invention," filed concurrently herewith and incorporated herein by reference, for a discussion of this issue.

to the Count are unpatentable to Moss, and Moss should not be accorded the benefit of their prior applications. Therefore, Paoletti should be awarded priority of invention, and such award is respectfully requested.[4]

Respectfully submitted,

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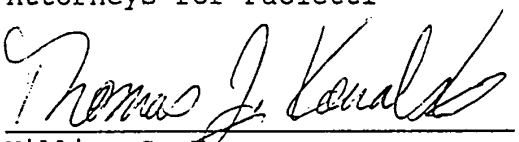

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[4] To any extent necessary, this Motion is also to be construed as a Motion for an immediate testimony period on the issues of enablement, written description, clarity, definiteness, entitlement to benefit of earlier applications and patentability of Moss claims, and the art with respect thereto because immediate determination of these issues can determine which party is senior or junior (i.e., the burden of proof), and whether an Interference is necessary at all (because if Moss is not entitled to a filing date or is otherwise unable to overcome the prior art, there is no need for an Interference).

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CERTIFICATE OR SERVICE

The undersigned hereby certifies that a true copy of the foregoing PAOLETTI ET AL. MOTION UNDER 37 C.F.R. §1.633(a) AND (g) FOR JUDGMENT ON GROUND THAT MOSS ET AL. CLAIMS ARE NOT PATENTABLE TO MOSS ET AL. FOR FAILING TO PROVIDE AN ENABLING DISCLOSURE AND AN ADEQUATE WRITTEN DESCRIPTION is being served upon the party MOSS ET AL. on this 13th day of March, 1995 by posting said true copy by first class mail, postage prepaid to the lead attorney for MOSS ET AL. at his address of record, namely:

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